



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification 7 : C12N 15/31, 15/62, C07K 14/315, A61K 39/09</p>	A2	<p>(11) International Publication Number: WO 00/39299</p> <p>(43) International Publication Date: 6 July 2000 (06.07.00)</p>																																																																																																																																																																									
<p>(21) International Application Number: PCT/CA99/01218</p> <p>(22) International Filing Date: 20 December 1999 (20.12.99)</p> <p>(30) Priority Data: 60/113,800 23 December 1998 (23.12.98) US</p> <p>(71) Applicant (for all designated States except US): BIOCHEM PHARMA INC. [CA/CA]; 275 Armand Frappier Boulevard, Laval, Québec H7V 4A7 (CA).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): HAMEL, Josée [CA/CA]; (CA). BRODEUR, Bernard, R. [CA/CA]; 2401 Maritain, Sillery, Québec G1T 1N6 (CA). PINEAU, Isabelle [CA/CA]; 3035 Rue des Châtelets, Sainte-Foy, Québec G1V 3Y7 (CA). MARTIN, Denis [CA/CA]; 4728-G Gaboury, St-Augustin-DesMoures, Québec G3A 1E9 (CA). RIOUX, Clément [CA/CA]; 12 Croissant Barabé, Ile Bizard, Québec H9E 1J1 (CA). CHARLAND, Nathalie [CA/CA]; 4340 Rue du Rapide, Apt. 8, Charny, Québec J6X 3N6 (CA).</p> <p>(74) Agents: MURPHY, Kevin, P. et al.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montreal, Québec H3A 2Y3 (CA).</p>																																																																																																																																																																											
<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>																																																																																																																																																																											
<p>(54) Title: NOVEL STREPTOCOCCUS ANTIGENS</p> <table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td>BVH11-2 SP64</td> <td>BVH11 SP63</td> <td>BVH11 JNR.7/87</td> <td>BVH11-2 JNR.7/87</td> <td>BVH11 WU2</td> <td>BVH11-2 WU2</td> <td>BVH11 A66</td> <td>BVH11-2 A66</td> <td>BVH11 P4241</td> <td>BVH11-2 P4241</td> <td>BVH11 Rz-1</td> <td>BVH11-2 Rz-1</td> <td>BVH11 SP64</td> </tr> <tr> <td>181% S 86%</td> <td>188% S 90%</td> <td>188% S 91%</td> <td>182% S 87%</td> <td>180% S 85%</td> <td>180% S 85%</td> <td>180% S 85%</td> <td>180% S 85%</td> <td>180% S 85%</td> <td>180% S 85%</td> <td>188% S 91%</td> <td>181% S 85%</td> <td>BVH11 SP64</td> </tr> <tr> <td></td> <td>187% S 90%</td> <td>187% S 90%</td> <td>198% S 98%</td> <td>195% S 96%</td> <td>196% S 97%</td> <td>195% S 96%</td> <td>196% S 97%</td> <td>195% S 96%</td> <td>196% S 97%</td> <td>187% S 90%</td> <td>194% S 95%</td> <td>BVH11-2 SP64</td> </tr> <tr> <td></td> <td></td> <td>196% S 96%</td> <td>188% S 91%</td> <td>188% S 90%</td> <td>187% S 91%</td> <td>188% S 90%</td> <td>187% S 91%</td> <td>188% S 90%</td> <td>187% S 91%</td> <td>197% S 90%</td> <td>189% S 91%</td> <td>BVH11 SP63</td> </tr> <tr> <td></td> <td></td> <td></td> <td>187% S 90%</td> <td>187% S 90%</td> <td>186% S 91%</td> <td>187% S 90%</td> <td>186% S 91%</td> <td>187% S 90%</td> <td>186% S 91%</td> <td>196% S 96%</td> <td>188% S 90%</td> <td>BVH11 JNR.7/87</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td>196% S 97%</td> <td>197% S 98%</td> <td>197% S 97%</td> <td>196% S 98%</td> <td>197% S 97%</td> <td>196% S 98%</td> <td>187% S 90%</td> <td>194% S 95%</td> <td>BVH11-2 JNR.7/87</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td>198% S 98%</td> <td>192% S 94%</td> <td>198% S 98%</td> <td>199% S 99%</td> <td>198% S 98%</td> <td>187% S 91%</td> <td>192% S 94%</td> <td>BVH11 WU2</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>198% S 98%</td> <td>199% S 99%</td> <td>198% S 98%</td> <td>199% S 99%</td> <td>186% S 90%</td> <td>193% S 95%</td> <td>BVH11-2 WU2</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>199% S 99%</td> <td>199% S 99%</td> <td>199% S 99%</td> <td>187% S 91%</td> <td>192% S 94%</td> <td>BVH11 A66</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>199% S 99%</td> <td>199% S 99%</td> <td>186% S 90%</td> <td>193% S 95%</td> <td>BVH11-2 A66</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>199% S 99%</td> <td>187% S 91%</td> <td>192% S 94%</td> <td>BVH11 P4241</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>186% S 90%</td> <td>193% S 95%</td> <td>BVH11-2 P4241</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>191% S 92%</td> <td>BVH11 Rz-1</td> </tr> </table>			BVH11-2 SP64	BVH11 SP63	BVH11 JNR.7/87	BVH11-2 JNR.7/87	BVH11 WU2	BVH11-2 WU2	BVH11 A66	BVH11-2 A66	BVH11 P4241	BVH11-2 P4241	BVH11 Rz-1	BVH11-2 Rz-1	BVH11 SP64	181% S 86%	188% S 90%	188% S 91%	182% S 87%	180% S 85%	180% S 85%	180% S 85%	180% S 85%	180% S 85%	180% S 85%	188% S 91%	181% S 85%	BVH11 SP64		187% S 90%	187% S 90%	198% S 98%	195% S 96%	196% S 97%	195% S 96%	196% S 97%	195% S 96%	196% S 97%	187% S 90%	194% S 95%	BVH11-2 SP64			196% S 96%	188% S 91%	188% S 90%	187% S 91%	188% S 90%	187% S 91%	188% S 90%	187% S 91%	197% S 90%	189% S 91%	BVH11 SP63				187% S 90%	187% S 90%	186% S 91%	187% S 90%	186% S 91%	187% S 90%	186% S 91%	196% S 96%	188% S 90%	BVH11 JNR.7/87					196% S 97%	197% S 98%	197% S 97%	196% S 98%	197% S 97%	196% S 98%	187% S 90%	194% S 95%	BVH11-2 JNR.7/87						198% S 98%	192% S 94%	198% S 98%	199% S 99%	198% S 98%	187% S 91%	192% S 94%	BVH11 WU2							198% S 98%	199% S 99%	198% S 98%	199% S 99%	186% S 90%	193% S 95%	BVH11-2 WU2								199% S 99%	199% S 99%	199% S 99%	187% S 91%	192% S 94%	BVH11 A66									199% S 99%	199% S 99%	186% S 90%	193% S 95%	BVH11-2 A66										199% S 99%	187% S 91%	192% S 94%	BVH11 P4241											186% S 90%	193% S 95%	BVH11-2 P4241												191% S 92%	BVH11 Rz-1
BVH11-2 SP64	BVH11 SP63	BVH11 JNR.7/87	BVH11-2 JNR.7/87	BVH11 WU2	BVH11-2 WU2	BVH11 A66	BVH11-2 A66	BVH11 P4241	BVH11-2 P4241	BVH11 Rz-1	BVH11-2 Rz-1	BVH11 SP64																																																																																																																																																															
181% S 86%	188% S 90%	188% S 91%	182% S 87%	180% S 85%	180% S 85%	180% S 85%	180% S 85%	180% S 85%	180% S 85%	188% S 91%	181% S 85%	BVH11 SP64																																																																																																																																																															
	187% S 90%	187% S 90%	198% S 98%	195% S 96%	196% S 97%	195% S 96%	196% S 97%	195% S 96%	196% S 97%	187% S 90%	194% S 95%	BVH11-2 SP64																																																																																																																																																															
		196% S 96%	188% S 91%	188% S 90%	187% S 91%	188% S 90%	187% S 91%	188% S 90%	187% S 91%	197% S 90%	189% S 91%	BVH11 SP63																																																																																																																																																															
			187% S 90%	187% S 90%	186% S 91%	187% S 90%	186% S 91%	187% S 90%	186% S 91%	196% S 96%	188% S 90%	BVH11 JNR.7/87																																																																																																																																																															
				196% S 97%	197% S 98%	197% S 97%	196% S 98%	197% S 97%	196% S 98%	187% S 90%	194% S 95%	BVH11-2 JNR.7/87																																																																																																																																																															
					198% S 98%	192% S 94%	198% S 98%	199% S 99%	198% S 98%	187% S 91%	192% S 94%	BVH11 WU2																																																																																																																																																															
						198% S 98%	199% S 99%	198% S 98%	199% S 99%	186% S 90%	193% S 95%	BVH11-2 WU2																																																																																																																																																															
							199% S 99%	199% S 99%	199% S 99%	187% S 91%	192% S 94%	BVH11 A66																																																																																																																																																															
								199% S 99%	199% S 99%	186% S 90%	193% S 95%	BVH11-2 A66																																																																																																																																																															
									199% S 99%	187% S 91%	192% S 94%	BVH11 P4241																																																																																																																																																															
										186% S 90%	193% S 95%	BVH11-2 P4241																																																																																																																																																															
											191% S 92%	BVH11 Rz-1																																																																																																																																																															
<p>(57) Abstract</p> <p>Streptococcus proteins and polynucleotides encoding them are disclosed. Said proteins are antigenic and therefore useful vaccine components for the prophylaxis or therapy of streptococcus infection in animals. Also disclosed are recombinant methods of producing the protein antigens as well as diagnostic assays for detecting streptococcus bacterial infection.</p>																																																																																																																																																																											

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

NOVEL STREPTOCOCCUS ANTIGENS

FIELD OF THE INVENTION

- 5 The present invention is related to antigens, more particularly protein antigens of streptococcus pneumoniae pathogen which are useful as vaccine components for therapy and/or prophylaxis.

10 **BACKGROUND OF THE INVENTION**

- S. pneumoniae is an important agent of disease in man especially among infants, the elderly and immunocompromised persons. It is a bacterium frequently isolated from
- 15 patients with invasive diseases such as bacteraemia/septicaemia, pneumonia, meningitis with high morbidity and mortality throughout the world. Even with appropriate antibiotic therapy, pneumococcal infections still result in many deaths. Although the advent of
- 20 antimicrobial drugs has reduced the overall mortality from pneumococcal disease, the presence of resistant pneumococcal organisms has become a major problem in the world today. Effective pneumococcal vaccines could have a major impact on the morbidity and mortality associated with S. pneumoniae
- 25 disease. Such vaccines would also potentially be useful to prevent otitis media in infants and young children.

- Efforts to develop a pneumococcal vaccine have generally concentrated on generating immune responses to the
- 30 pneumococcal capsular polysaccharide. More than 80 pneumococcal capsular serotypes have been identified on the basis of antigenic differences. The currently available pneumococcal vaccine, comprising 23 capsular polysaccharides

that most frequently caused disease, has significant shortcomings related primarily to the poor immunogenicity of some capsular polysaccharides, the diversity of the serotypes and the differences in the distribution of serotypes over time, geographic areas and age groups. In particular, the failure of existing vaccines and capsular conjugate vaccines currently in development to protect young children against all serotypes spurres evaluation of other S. pneumoniae components. Although immunogenicity of capsular polysaccharides can be improved, serotype specificity will still represent a major limitation of polysaccharide-based vaccines. The use of a antigenically conserved immunogenic pneumococcal protein antigen, either by itself or in combination with additional components, offers the possibility of a protein-based pneumococcal vaccine.

PCT Publication number WO98/18930 published may 7 1998 entitled "*Streptococcus Pneumoniae* antigens and vaccines" describes certain polypeptides which are claimed to be antigenic. However, no biological activity of these polypeptides is reported.

Therefore their remains an unmet need for *Streptococcus* antigens that may be used as vaccine components for the prophylaxis and/or therapy of *Streptococcus* infection.

SUMMARY OF THE INVENTION

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 4, 6, 8, 10, 14, 16, 55

to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

5 In other aspects, there are provided vectors comprising polynucleotides of the invention operably linked to an expression control region, as well as host cells transfected with said vectors and methods of producing polypeptides comprising culturing said host cells under conditions suitable for expression.

10

In yet another aspect, there are provided novel polypeptides encoded by polynucleotides of the invention.

15 **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 is the DNA sequence of BVH-3 gene; SEQ ID NO: 1.

20 Figure 2 is the amino acid sequence of BVH-3 protein; SEQ ID NO: 2.

Figure 3 is the DNA sequence of BVH-11 gene; SEQ ID NO: 3.

25 Figure 4 is the amino acid sequence of BVH-11 protein; SEQ ID NO: 4.

Figure 5 is the DNA sequence of BVH-28 gene; SEQ ID NO: 5.

30 Figure 6 is the amino acid sequence of BVH-28 protein; SEQ ID NO: 6.

Figure 7 is the DNA sequence of BVH-3A gene which corresponds to the 5' terminal end of BVH-3; SEQ ID NO: 7.

Figure 8 is the amino acid sequence of BVH-3A protein; **SEQ ID NO: 8.**

Figure 9 is the DNA sequence of BVH-3B gene which
5 corresponds to the 3' terminal end of BVH-3; **SEQ ID NO: 9.**

Figure 10 is the amino acid sequence of BVH-3B protein; **SEQ ID NO: 10.**

10 Figure 11 depicts the comparison of the predicted amino acid sequences of the BVH-3 open reading frames from WU2, RX1, JNR.7/87, SP64, P4241 and A66 S. pneumoniae strains by using the program Clustal W from MacVector sequence
15 analysis software (version 6.5). Underneath the alignment, there is a consensus line where * and . characters indicate identical and similar amino acid residues, respectively.

Figure 12 depicts the comparison of the predicted amino
20 acid sequences of the BVH-11 open reading frames from WU2, Rx1, JNR.7/87, SP64, P4241, A66 and SP63 S. pneumoniae strains by using the program Clustal W from MacVector sequence analysis software (version 6.5). Underneath the alignment, there is a consensus line where * and .
25 characters indicate identical and similar amino acid residues, respectively.

Figure 13 depicts the comparison of the predicted amino acid sequences of the BVH-11 proteins from various S. pneumoniae strains. The degrees of identity (I) and
30 similarity (S) were determined by using the program Clustal W from MacVector sequence analysis software (version 6.5).

Figure 14 is a DNA sequence containing the complete BVH-3
35 gene (open reading frame "ORF" at nucleotides 1777 to 4896); **SEQ ID NO: 11.**

Figure 15 is a DNA sequence containing the complete BVH-11 gene (ORF at nucleotides 45 to 2567); **SEQ ID NO: 12.**

- 5 Figure 16 is a DNA sequence containing the complete BVH-11-2 gene (ORF at nucleotides 114 to 2630); **SEQ ID NO: 13.**

Figure 17 is the amino acid sequence of BVH-11-2 protein;
SEQ ID NO: 14.

10

Figure 18 is the DNA sequence of SP63 BVH-3 gene; **SEQ ID NO:15.**

- Figure 19 is the amino acid sequence of SP63 BVH-3 protein;
15 **SEQ ID NO: 16.**

Figure 20 is the amino acid sequence of BVH-3M protein; **SEQ ID NO: 55.**

- 20 Figure 21 is the amino acid sequence of BVH-3AD protein;
SEQ ID NO: 56.

Figure 22 is the amino acid sequence of L-BVH-3-AD protein;
SEQ ID NO: 57.

25

Figure 23 is the amino acid sequence of NEW12 protein; **SEQ ID NO: 58.**

- Figure 24 is the amino acid sequence of BVH-3C protein; **SEQ ID NO: 59.**

30

Figure 25 is the amino acid sequence of BVH-11M protein;
SEQ ID NO: 60.

- 35 Figure 26 is the amino acid sequence of BVH-11A protein;
SEQ ID NO: 61.

Figure 27 is the amino acid sequence of BVH-11B (also called New13) protein; **SEQ ID NO: 62.**

- 5 Figure 28 is the amino acid sequence of BVH-11C protein; **SEQ ID NO: 63.**

Figure 29 is the amino acid sequence of NEW1 protein; **SEQ ID NO: 64.**

10

Figure 30 is the amino acid sequence of NEW2 protein; **SEQ ID NO: 65.**

- 15 Figure 31 is the amino acid sequence of NEW3 protein; **SEQ ID NO: 66.**

Figure 32 is the amino acid sequence of NEW4 protein; **SEQ ID NO: 67.**

- 20 Figure 33 is the amino acid sequence of NEW5 protein; **SEQ ID NO: 68.**

Figure 34 is the amino acid sequence of NEW6 protein; **SEQ ID NO: 69.**

25

Figure 35 is the amino acid sequence of NEW7 protein; **SEQ ID NO: 70.**

- 30 Figure 36 is the amino acid sequence of NEW8 protein; **SEQ ID NO: 71.**

Figure 37 is the amino acid sequence of NEW9 protein; **SEQ ID NO: 72.**

- 35 Figure 38 is the amino acid sequence of BVH-11-2M protein; **SEQ ID NO: 73.**

Figure 39 is the amino acid sequence of NEW10 protein; **SEQ ID NO: 74.**

5 Figure 40 is the amino acid sequence of NEW11 protein; **SEQ ID NO: 75.**

Figure 41 is the DNA sequence of NEW12 gene; **SEQ ID NO: 76.**

10 Figure 42 is the amino acid sequence of NEW14 protein; **SEQ ID NO: 77.**

Figure 43 is the amino acid sequence of NEW15 protein; **SEQ ID NO: 78.**

15

Figure 44 is the amino acid sequence of NEW16 protein; **SEQ ID NO: 79.**

20 Figure 45 is the DNA sequence of GBS BVH-71 gene; **SEQ ID NO: 80.**

Figure 46 is the amino acid sequence of GBS BVH-71 protein; **SEQ ID NO: 81.**

25 Figure 47 is the DNA sequence of GAS BVH-71 gene; **SEQ ID NO: 82.**

Figure 48 is the amino acid sequence of GAS BVH-71 protein; **SEQ ID NO: 83.**

30

DETAILED DESCRIPTION OF THE INVENTION

35 According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from **SEQ ID NOs: 2, 4, 6, 8, 10, 14, 16, 55**

to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

5 According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 95% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

10

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 4, 8, 10, 14, 16, 55 to 15 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

20 According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 4, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

25 According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 4, 8, 10, 14, 16, 55 to 75, 77 to 79 or fragments, analogs or derivatives thereof.

30

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 8, 10, 16, 55, 56, 57, 35 58, 59, 64, 65, 66, 78 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 8, 10, 16, 55, 56, 57, 59, 64, 65, 66, 78 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 4, 14, 58, 60, 61, 62, 63, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 79 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 4, 14, 60, 61, 62, 63, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 79 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 4, 10, 14, 16, 55 to 75, 77 to 79 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence chosen from SEQ ID NOs: 10, 55 to 75, 77, 78, 79 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an

isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence chosen from **SEQ ID NOs: 55 to 75, 77, 78, 79** or fragments, analogs or derivatives thereof.

5

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from **SEQ ID NOs: 2, 4, 6, 8, 10** or

10

fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from **SEQ ID NOs: 2, 4, 10, 14, 16** or fragments, analogs or derivatives thereof.

15

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from **SEQ ID NOs: 2, 4, 14, 16** or fragments, analogs or derivatives thereof.

20

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 2** or fragments, analogs or derivatives thereof.

25

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 4** or fragments, analogs or derivatives thereof.

30

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence SEQ ID NO: 10 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence SEQ ID NO: 14 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence SEQ ID NO: 16 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence SEQ ID NO: 58 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence SEQ ID NO: 60 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence SEQ ID NO: 62 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 64** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 67** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 68** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 69** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 72** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 74** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 77** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from **SEQ ID NOS: 2, 4, 6, 8, 10** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from **SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from **SEQ ID NOS: 2, 4, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from **SEQ ID NOS: 2, 4, 10, 14, 16, 55 to 75, 77 to 79, 81, 83** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from **SEQ ID NOS: 2, 4, 8, 10, 14, 16, 55 to 75, 77 to 79** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from **SEQ ID NOS: 2, 4, 10, 14, 16, 55 to 75, 77 to 79** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from **SEQ ID NOS: 2, 4, 10, 14, 16** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 2** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 4** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 10** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 14** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 16** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from **SEQ ID NOS: 10, 55 to 75, 77, 78, 79** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NO: 10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof.

5

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NO: 10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof.

10

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NO: 10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof.

15

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NO: 10, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof.

20

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence SEQ ID NO: 58 or fragments, analogs or derivatives thereof.

25

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence SEQ ID NO: 62 or fragments, analogs or derivatives thereof.

30

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence

SEQ ID NO: 64 or fragments, analogs or

- polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 67** or fragments, analogs or derivatives thereof.
- 5 According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 68** or fragments, analogs or derivatives thereof.
- 10 According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 74** or fragments, analogs or derivatives thereof.
- 15 According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 77** or fragments, analogs or derivatives thereof.
- 20 In a further embodiment, the present invention also relates to chimeric polypeptides which comprise one or more polypeptides or fragments, analogs or derivatives thereof as described in the present application.
- 25 In a further embodiment, the present invention also relates to chimeric polypeptides which comprise one or more polypeptides or fragments, analogs or derivatives thereof as defined in the figures of the present application.
- 30 In a further embodiment, the present application also relates to chimeric polypeptides which comprise two or more polypeptides chosen from **SEQ ID NOs: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83** or fragments, analogs or derivatives thereof ;provided that the polypeptides or
- 35 fragments, analogs or derivatives thereof are linked as to form a chimeric polypeptide.

In a further embodiment, the chimeric polypeptide will comprise two or more polypeptides chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or
5 fragments, analogs or derivatives thereof; provided that the polypeptides or fragments, analogs or derivatives thereof are linked as to form a chimeric polypeptide.

In a further embodiment, the chimeric polypeptide will
10 comprise two or more polypeptides chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof; provided that the polypeptides or fragments, analogs or derivatives thereof are linked as to form a chimeric polypeptide.

15 In a further embodiment, the chimeric polypeptide will comprise two or more polypeptides chosen from SEQ ID NOS :10, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof; provided that the polypeptides or
20 fragments, analogs or derivatives thereof are linked as to form a chimeric polypeptide.

In a further embodiment, the chimeric polypeptide will comprise between 2 and 5 polypeptides.

25 In a further embodiment, the chimeric polypeptide will comprise between 2 and 4 polypeptides.

In a further embodiment, the chimeric polypeptide will
30 comprise between 2 and 3 polypeptides.

In a further embodiment, the chimeric polypeptide will comprise 2 polypeptides.

35

In a further embodiment, there is provided a chimeric polypeptide of formula (I):

A-(B)_m-(C)_n-D (I)

5 Wherein;

m is 0 or 1,

n is 0 or 1,

A is chosen from **SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83** or fragments, analogs or derivatives

10 thereof;

B is chosen from **SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83** or fragments, analogs or derivatives thereof;

C is chosen from **SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83** or fragments, analogs or derivatives thereof; and

15 **D** is chosen from **SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83** or fragments, analogs or derivatives thereof.

20

 In a further embodiment,

A is chosen from **SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77** or fragments, analogs or derivatives thereof;

25 **B** is chosen from **SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77**, or fragments, analogs or derivatives thereof;

C is chosen from **SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77** or fragments, analogs or derivatives

30 thereof; and

D is chosen from **SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77** or fragments, analogs or derivatives thereof.

35 In a further embodiment,

- A is chosen from SEQ ID NOs :10, 58, 60, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof;
B is chosen from SEQ ID NOs :10, 58, 60, 62, 64, 67, 68, 74, 77, or fragments, analogs or derivatives thereof;
5 C is chosen from SEQ ID NOs :10, 58, 60, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof; and
D is chosen from SEQ ID NOs :10, 58, 60, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof.
- 10 In one embodiment, chimeric polypeptides of the present invention comprise those wherein the following embodiments are present, either independently or in combination.
- In a further embodiment, A is SEQ ID NOs :10, 58, 62, 64,
15 67, 68, 74, 77 or fragments, analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :10 or fragments, analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :58 or fragments,
20 analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :62 or fragments, analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :64 or fragments, analogs or derivatives thereof.
- 25 In a further embodiment, A is SEQ ID NO :67 or fragments, analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :68 or fragments, analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :74 or fragments,
30 analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :77 or fragments, analogs or derivatives thereof.

In a further embodiment, B is SEQ ID NOS :10, 58, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof.

5 In a further embodiment, B is SEQ ID NO :10 or fragments, analogs or derivatives thereof.

In a further embodiment, B is SEQ ID NO :58 or fragments, analogs or derivatives thereof.

In a further embodiment, B is SEQ ID NO :64 or fragments, analogs or derivatives thereof.

10 In a further embodiment, B is SEQ ID NO :64 or fragments, analogs or derivatives thereof.

In a further embodiment, B is SEQ ID NO :67 or fragments, analogs or derivatives thereof.

15 In a further embodiment, B is SEQ ID NO :68 or fragments, analogs or derivatives thereof.

In a further embodiment, B is SEQ ID NO :74 or fragments, analogs or derivatives thereof.

In a further embodiment, B is SEQ ID NO : 77 or fragments, analogs or derivatives thereof.

20

In a further embodiment, C is SEQ ID NOS :10, 58, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof.

25 In a further embodiment, C is SEQ ID NO :10 or fragments, analogs or derivatives thereof.

In a further embodiment, C is SEQ ID NO :58 or fragments, analogs or derivatives thereof.

In a further embodiment, C is SEQ ID NO : 62 or fragments, analogs or derivatives thereof.

30 In a further embodiment, C is SEQ ID NO :64 or fragments, analogs or derivatives thereof.

In a further embodiment, C is SEQ ID NO : 67 or fragments, analogs or derivatives thereof.

In a further embodiment, C is SEQ ID NO : 68 or fragments,

analog or derivatives thereof.

In a further embodiment, C is SEQ ID NO : 74 or fragments, analog or derivatives thereof.

In a further embodiment, C is SEQ ID NO : 77 or fragments,
5 analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :10, 58, 62, 64, 67, 68, 74, 77 or fragments, analog or derivatives thereof.

10 In a further embodiment, D is SEQ ID NO :10 or fragments, analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :58 or fragments, analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :62 or fragments,
15 analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :64 or fragments, analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :67 or fragments, analog or derivatives thereof.

20 In a further embodiment, D is SEQ ID NO :68 or fragments, analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :74 or fragments, analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :77 or fragments,
25 analog or derivatives thereof.

In a further embodiment, m is 0.

In a further embodiment, n is 0.

30

In a further embodiment, m and n are 0.

In a further embodiment, m and n are 0, A is SEQ ID NO:64 or fragments, analog or derivatives thereof, B is SEQ ID

NO:62 or fragments, analogs or derivatives thereof.

In a further embodiment, *m* and *n* are 0, *A* is SEQ ID NO:62 or fragments, analogs or derivatives thereof, *B* is SEQ ID NO:64 or fragments, analogs or derivatives thereof.

5

In accordance with the present invention, all nucleotides encoding polypeptides and chimeric polypeptides are within the scope of the present invention.

- 10 In a further embodiment, the polypeptides or chimeric polypeptides in accordance with the present invention are antigenic.

- In a further embodiment, the polypeptides or chimeric
15 polypeptides in accordance with the present invention can elicit an immune response in an individual.

- In a further embodiment, the present invention also relates to polypeptides which are able to raise antibodies having
20 binding specificity to the polypeptides or chimeric polypeptides of the present invention as defined above.

- An antibody that "has binding specificity" is an antibody that recognizes and binds the selected polypeptide but
25 which does not substantially recognize and bind other molecules in a sample, e.g., a biological sample, which naturally includes the selected peptide. Specific binding can be measured using an ELISA assay in which the selected polypeptide is used as an antigen.

30

- Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent
35 applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In

case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

5

As used herein, "fragments", "derivatives" or "analogs" of the polypeptides of the invention include those polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably conserved) and which may be natural or unnatural. In one embodiment, derivatives and analogs of polypeptides of the invention will have about 70% identity with those sequences illustrated in the figures or fragments thereof. That is, 70% of the residues are the same. In a further embodiment, polypeptides will have greater than 75% homology. In a further embodiment, polypeptides will have greater than 80% homology. In a further embodiment, polypeptides will have greater than 85% homology. In a further embodiment, polypeptides will have greater than 90% homology. In a further embodiment, polypeptides will have greater than 95% homology. In a further embodiment, polypeptides will have greater than 99% homology. In a further embodiment, derivatives and analogs of polypeptides of the invention will have fewer than about 20 amino acid residue substitutions, modifications or deletions and more preferably less than 10. Preferred substitutions are those known in the art as conserved i.e. the substituted residues share physical or chemical properties such as hydrophobicity, size, charge or functional groups.

35

In accordance with the present invention, polypeptides of the invention include both polypeptides and chimeric polypeptides.

Also included are polypeptides which have fused thereto

other compounds which alter the polypeptides biological or pharmacological properties i.e. polyethylene glycol (PEG) to increase half-life; leader or secretory amino acid sequences for ease of purification; prepro- and pro- sequences; and (poly)saccharides.

Furthermore, in those situations where amino acid regions are found to be polymorphic, it may be desirable to vary one or more particular amino acids to more effectively mimic the different epitopes of the different streptococcus strains.

Moreover, the polypeptides of the present invention can be modified by terminal $-NH_2$ acylation (eg. by acetylation, or thioglycolic acid amidation, terminal carboxy amidation, e.g. with ammonia or methylamine) to provide stability, increased hydrophobicity for linking or binding to a support or other molecule.

Also contemplated are hetero and homo polypeptide multimers of the polypeptide fragments, analogues and derivatives. These polymeric forms include, for example, one or more polypeptides that have been cross-linked with cross-linkers such as avidin/biotin, gluteraldehyde or dimethylsuperimide. Such polymeric forms also include polypeptides containing two or more tandem or inverted contiguous sequences, produced from multicistronic mRNAs generated by recombinant DNA technology. Preferably, a fragment, analog or derivative of a polypeptide of the invention will comprise at least one antigenic region i.e. at least one epitope.

In order to achieve the formation of antigenic polymers (i.e. synthetic multimers), polypeptides may be utilized having bishaloacetyl groups, nitroarylhalides, or the like, where the reagents being specific for thio groups.

Therefore, the link between two mercapto groups of the different peptides may be a single bond or may be composed of a linking group of at least two, typically at least four, and not more than 16, but usually not more than about 14 carbon atoms.

In a particular embodiment, polypeptide fragments, analogs and derivatives of the invention do not contain a methionine (Met) starting residue. Preferably, polypeptides will not incorporate a leader or secretory sequence (signal sequence). The signal portion of a polypeptide of the invention may be determined according to established molecular biological techniques. In general, the polypeptide of interest may be isolated from a streptococcus culture and subsequently sequenced to determine the initial residue of the mature protein and therefore the sequence of the mature polypeptide.

According to another aspect, there are provided vaccine compositions comprising one or more streptococcus polypeptides of the invention in admixture with a pharmaceutically acceptable carrier diluent or adjuvant. Suitable adjuvants include oils i.e. Freund's complete or incomplete adjuvant; salts i.e. $\text{AlK}(\text{SO}_4)_3$, $\text{AlNa}(\text{SO}_4)_2$, $\text{AlNH}_4(\text{SO}_4)_2$, silica, kaolin, carbon polynucleotides i.e. poly IC and poly AU. Preferred adjuvants include QuilA and Alhydrogel. Vaccines of the invention may be administered parenterally by injection, rapid infusion, nasopharyngeal absorption, dermoabsorption, or bucal or oral. Pharmaceutically acceptable carriers also include tetanus toxoid.

Vaccine compositions of the invention are used for the treatment or prophylaxis of streptococcus infection and/or diseases and symptoms mediated by streptococcus infection as described in P.R. Murray (Ed, in chief), E.J. Baron, M.A.

- Pfaller, F.C. Tenover and R.H. Yolken. Manual of Clinical Microbiology, ASM Press, Washington, D.C. sixth edition, 1995, 1482p which are herein incorporated by reference. In one embodiment, vaccine compositions of the present
- 5 invention are used for the treatment or prophylaxis of meningitis, otitis media, bacteremia or pneumonia. In one embodiment, vaccine compositions of the invention are used for the treatment or prophylaxis of *streptococcus* infection and/or diseases and symptoms mediated by *streptococcus*
- 10 infection, in particular *S.pneumoniae*, group A *streptococcus* (*pyogenes*), group B *streptococcus* (GBS or *agalactiae*), *dysgalactiae*, *uberis*, *nocardia* as well as *Staphylococcus aureus*. In a further embodiment, the *streptococcus* infection is *S.pneumoniae*.
- 15 In a particular embodiment, vaccines are administered to those individuals at risk of *streptococcus* infection such as infants, elderly and immunocompromised individuals.
- 20 As used in the present application, the term " individuals" include mammals. In a further embodiment, the mammal is human.
- Vaccine compositions are preferably in unit dosage form of
- 25 about 0.001 to 100 µg/kg (antigen/body weight) and more preferably 0.01 to 10 µg/kg and most preferably 0.1 to 1 µg/kg 1 to 3 times with an interval of about 1 to 6 week intervals between immunizations.
- 30 According to another aspect, there are provided polynucleotides encoding polypeptides characterized by the amino'acid sequence chosen from SEQ ID NOs: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.
- 35

In one embodiment, polynucleotides are those illustrated in
SEQ ID Nos: 1, 3, 5, 7, 9, 11, 12, 13, 15, 76, 80, 82

which may include the open reading frames (ORF), encoding
polypeptides of the invention. It will be appreciated that
5 the polynucleotide sequences illustrated in the figures may
be altered with degenerate codons yet still encode the
polypeptides of the invention. Accordingly the present
invention further provides polynucleotides which hybridize
to the polynucleotide sequences herein above described (or
10 the complement sequences thereof) having 50% identity
between sequences. In one embodiment, at least 70% identity
between sequences. In one embodiment, at least 75% identity
between sequences. In one embodiment, at least 80% identity
between sequences. In one embodiment, at least 85% identity
15 between sequences. In one embodiment, at least 90% identity
between sequences. In a further embodiment, polynucleotides
are hybridizable under stringent conditions i.e. having at
least 95% identity. In a further embodiment, more than 97%
identity.

20

In a further embodiment, polynucleotides are those
illustrated in SEQ ID NOs : 1, 3, 7, 9, 11, 12, 13, 15, 76,
80, 82 encoding polypeptides of the invention.

25 In a further embodiment, polynucleotides are those
illustrated in SEQ ID NOs : 1, 3, 9, 11, 12, 13, 15, 76,
80, 82 which may include the open reading frames (ORF),
encoding polypeptides of the invention.

30 In a further embodiment, polynucleotides are those

illustrated in SEQ ID NOs : 1, 3, 9, 11, 12, 13, 15, 76

illustrated in **SEQ ID NOS : 1, 3, 7, 9, 11, 12, 13, 15, 76** which may include the open reading frames (ORF), encoding polypeptides of the invention.

- 5 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NOS : 1, 7, 9, 11, 15, 76** which may include the open reading frames (ORF), encoding polypeptides of the invention.
- 10 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NOS : 1, 9, 11, 15, 76** which may include the open reading frames (ORF), encoding polypeptides of the invention.
- 15 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NOS : 1, 7, 9, 11** which may include the open reading frames (ORF), encoding polypeptides of the invention.
- 20 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO : 1**, encoding polypeptides of the invention.
- In a further embodiment, polynucleotides are those
- 25 illustrated in **SEQ ID NO :7**, encoding polypeptides of the invention.
- In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO :9**, encoding polypeptides of the
- 30 invention.
- In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO :11**, encoding polypeptides of the invention.

35

In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO :15**, encoding polypeptides of the invention.

- 5 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NOS : 3, 12, 13, 76**, encoding polypeptides of the invention.

- 10 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO :3**, encoding polypeptides of the invention.

- 15 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO :12**, encoding polypeptides of the invention.

- 20 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO :13**, encoding polypeptides of the invention.

- In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO :76**, encoding polypeptides of the invention.

- 25 As will be readily appreciated by one skilled in the art, polynucleotides include both DNA and RNA.

- The present invention also includes polynucleotides complementary to the polynucleotides described in the present application.
- 30

- In a further aspect, polynucleotides encoding polypeptides of the invention, or fragments, analogs or derivatives thereof, may be used in a DNA immunization method. That is, they can be incorporated into a vector which is
- 35

replicable and expressible upon injection thereby producing the antigenic polypeptide in vivo. For example polynucleotides may be incorporated into a plasmid vector under the control of the CMV promoter which is functional
5 in eukaryotic cells. Preferably the vector is injected intramuscularly.

According to another aspect, there is provided a process for producing polypeptides of the invention by recombinant
10 techniques by expressing a polynucleotide encoding said polypeptide in a host cell and recovering the expressed polypeptide product. Alternatively, the polypeptides can be produced according to established synthetic chemical techniques i.e. solution phase or solid phase synthesis of
15 oligopeptides which are ligated to produce the full polypeptide (block ligation).

General methods for obtention and evaluation of polynucleotides and polypeptides are described in the
20 following references: Sambrook et al, Molecular Cloning: A Laboratory Manual, 2nd ed, Cold Spring Harbor, N.Y., 1989; Current Protocols in Molecular Biology, Edited by Ausubel F.M. et al., John Wiley and Sons, Inc. New York; PCR Cloning Protocols, from Molecular Cloning to Genetic
25 Engineering, Edited by White B.A., Humana Press, Totowa, New Jersey, 1997, 490 pages; Protein Purification, Principles and Practices, Scopes R.K., Springer-Verlag, New York, 3rd Edition, 1993, 380 pages; Current Protocols in Immunology, Edited by Coligan J.E. et al., John Wiley &
30 Sons Inc., New York which are herein incorporated by reference.

For recombinant production, host cells are transfected with vectors which encode the polypeptide, and then cultured in
35 a nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the genes.

Suitable vectors are those that are viable and replicable in the chosen host and include chromosomal, non-chromosomal and synthetic DNA sequences e.g. bacterial plasmids, phage DNA, baculovirus, yeast plasmids, vectors derived from combinations of plasmids and phage DNA. The polypeptide sequence may be incorporated in the vector at the appropriate site using restriction enzymes such that it is operably linked to an expression control region comprising a promoter, ribosome binding site (consensus region or Shine-Dalgarno sequence), and optionally an operator (control element). One can select individual components of the expression control region that are appropriate for a given host and vector according to established molecular biology principles (Sambrook et al, Molecular Cloning: A Laboratory Manual, 2nd ed, Cold Spring Harbor, N.Y., 1989; Current Protocols in Molecular Biology, Edited by Ausubel F.M. et al., John Wiley and Sons, Inc. New York incorporated herein by reference). Suitable promoters include but are not limited to LTR or SV40 promoter, E.coli lac, tac or trp promoters and the phage lambda P_i promoter. Vectors will preferably incorporate an origin of replication as well as selection markers i.e. ampicillin resistance gene. Suitable bacterial vectors include pET, pQE70, pQE60, pQE-9, pbs, pD10 phagescript, psiX174, pbluescript SK, pbsks, pNH8A, pNH16a, pNH18A, pNH46A, ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 and eukaryotic vectors pBlueBacIII, pWLNEO, pSV2CAT, pOG44, pXT1, pSG, pSVK3, pBPV, pMSG and pSVL. Host cells may be bacterial i.e. E.coli, Bacillus subtilis, Streptomyces; fungal i.e. Aspergillus niger, Aspergillus nidulins; yeast i.e. Saccharomyces or eukaryotic i.e. CHO, COS.

Upon expression of the polypeptide in culture, cells are typically harvested by centrifugation then disrupted by physical or chemical means (if the expressed polypeptide is not secreted into the media) and the resulting crude

extract retained to isolate the polypeptide of interest. Purification of the polypeptide from culture media or lysate may be achieved by established techniques depending on the properties of the polypeptide i.e. using ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, hydroxylapatite chromatography and lectin chromatography. Final purification may be achieved using HPLC.

10 The polypeptide may be expressed with or without a leader or secretion sequence. In the former case the leader may be removed using post-translational processing (see US 4,431,739; US 4,425,437; and US 4,338,397 incorporated herein by reference) or be chemically removed subsequent to purifying the expressed polypeptide.

According to a further aspect, the streptococcus polypeptides of the invention may be used in a diagnostic test for streptococcus infection, in particular S. pneumoniae infection. Several diagnostic methods are possible, for example detecting streptococcus organism in a biological sample, the following procedure may be followed:

- a) obtaining a biological sample from a patient;
- 25 b) incubating an antibody or fragment thereof reactive with a streptococcus polypeptide of the invention with the biological sample to form a mixture; and
- c) detecting specifically bound antibody or bound fragment in the mixture which indicates the presence
- 30 of streptococcus.

Alternatively, a method for the detection of antibody specific to a streptococcus antigen in a biological sample containing or suspected of containing said antibody may be performed as follows:

- 35 a) obtaining a biological sample from a patient;

- b) incubating one or more streptococcus polypeptides of the invention or fragments thereof with the biological sample to form a mixture; and
- c) detecting specifically bound antigen or bound fragment in the mixture which indicates the presence of antibody specific to streptococcus.

One of skill in the art will recognize that this diagnostic test may take several forms, including an immunological test such as an enzyme-linked immunosorbent assay (ELISA), a radioimmunoassay or a latex agglutination assay, essentially to determine whether antibodies specific for the protein are present in an organism.

- 15 The DNA sequences encoding polypeptides of the invention may also be used to design DNA probes for use in detecting the presence of streptococcus in a biological sample suspected of containing such bacteria. The detection method of this invention comprises:
 - 20 a) obtaining the biological sample from a patient;
 - b) incubating one or more DNA probes having a DNA sequence encoding a polypeptide of the invention or fragments thereof with the biological sample to form a mixture; and
 - 25 c) detecting specifically bound DNA probe in the mixture which indicates the presence of streptococcus bacteria.

The DNA probes of this invention may also be used for detecting circulating streptococcus i.e. S.pneumoniae nucleic acids in a sample, for example using a polymerase chain reaction, as a method of diagnosing streptococcus infections. The probe may be synthesized using conventional techniques and may be immobilized on a solid phase, or may be labelled with a detectable label. A preferred DNA probe for this application is an oligomer

having a sequence complementary to at least about 6 contiguous nucleotides of the streptococcus pneumoniae polypeptides of the invention.

- 5 Another diagnostic method for the detection of streptococcus in a patient comprises:
- a) labelling an antibody reactive with a polypeptide of the invention or fragment thereof with a detectable label;
 - 10 b) administering the labelled antibody or labelled fragment to the patient; and
 - c) detecting specifically bound labelled antibody or labelled fragment in the patient which indicates the presence of streptococcus.

15

A further aspect of the invention is the use of the streptococcus polypeptides of the invention as immunogens for the production of specific antibodies for the diagnosis and in particular the treatment of streptococcus infection.

- 20 Suitable antibodies may be determined using appropriate screening methods, for example by measuring the ability of a particular antibody to passively protect against streptococcus infection in a test model. One example of an animal model is the mouse model described in the examples
- 25 herein. The antibody may be a whole antibody or an antigen-binding fragment thereof and may belong to any immunoglobulin class. The antibody or fragment may be of animal origin, specifically of mammalian origin and more specifically of murine, rat or human origin. It may be a
- 30 natural antibody or a fragment thereof, or if desired, a recombinant antibody or antibody fragment. The term recombinant antibody or antibody fragment means antibody or antibody fragment which was produced using molecular biology techniques. The antibody or antibody fragments may
- 35 be polyclonal, or preferably monoclonal. It may be specific for a number of epitopes associated with the

streptococcus pneumoniae polypeptides but is preferably specific for one.

Without limiting its scope, the present invention also
 5 relates to new antigens designated BVH-3, BVH-11, BVH-11-2, BVH-28 and BVH-71. The present invention also relates to truncated polypeptides comprising fragments of the new antigens designated BVH-3, BVH-11, BVH-11-2, BVH-28 and BVH-71. The present invention also relates to chimeric
 10 polypeptides comprising fragments of the new antigens designated BVH-3, BVH-11, BVH-11-2, BVH-28 and BVH-71. The following is a reference table summarizing the relation between the antigens of the present invention:

Family	Nucleotide SEQ ID NO	Polypeptide SEQ ID NO
BVH-3		
BVH-3	1, 11	2
BVH-3A	7	8
BVH-3B	9	10
BVH-3 SP63	15	16
BVH-3M		55
BVH-3AD		56
L-BVH-3AD		57
New12	76	58
BVH-3C		59
New1		64
New2		65
New3		66
New15		78
BVH-11		
BVH-11	3, 12	4
BVH-11-2	13	14
BVH-11M		60
BVH-11A		61
BVH-11B also referred to as NEW13		62
BVH-11C		63
New4		67
New5		68

Family	Nucleotide SEQ ID NO	Polypeptide SEQ ID NO
New6		69
New7		70
New8		71
New9		72
BVH-11-2M		73
New10		74
New11		75
New12	76	58
New14		77
New16		79
BVH-28		
BVH-28	5	6
BVH-71		
GBS	80	81
GAS	82	83

EXAMPLE 1

- 5 This example illustrates the cloning of S. pneumoniae genes.

The coding region of S. pneumoniae gene BVH-3 (SEQ ID NO: 1) and the coding region of S. pneumoniae gene BVH-28 (SEQ ID NO: 5) were amplified by PCR (DNA Thermal Cyclor GeneAmp

10 PCR system 2400 Perkin Elmer, San Jose, CA) from genomic DNA of serogroup 6 S. pneumoniae strain SP64 using the oligos that contained base extensions for the addition of restriction sites BglII (AGATCT) and XbaI (TCTAGA). PCR products were purified from agarose gel using a QIAquick gel

15 extraction kit from QIAgen (Chatsworth, CA), digested BglII-XbaI (Pharmacia Canada Inc, Baie d'Urfé, Canada), extracted with phenol : chloroform and precipitated with ethanol. The Superlinker vector pSL301 (Invitrogen, San Diego, CA) was digested with BglII and XbaI and purified from agarose gel

20 using a QIAquick gel extraction kit from QIAgen (Chatsworth, CA). The BglII-XbaI genomic DNA fragments were ligated to

the BglII-XbaI pSL301 vector. The ligated products were transformed into *E. coli* strain DH5a [f80 lacZ DM15 endA1 recA1 hsdR17 (^rK⁻K⁺) supE44 thi-11⁻ gyrA96 relA1 D(lacZYA-argF)U169] (Gibco BRL, Gaithersburg, MD) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). Recombinant pSL301 plasmids (rpSL301) containing either BVH-3 or BVH-28 gene were purified using a QIAGEN kit (Chatsworth, CA) and DNA inserts were confirmed by nucleotide sequence analysis (Taq Dye Deoxy Terminator Cycle Sequencing kit, ABI, Foster City, CA). Recombinant rpSL301 (rpSL301) were digested with the restriction enzymes BglII (AGATCT) and XhoI (CTCGAG). DNA fragments BglII-XhoI were purified using the QIAquick gel extraction kit from QIAGEN (Chatsworth, CA). pET-32c(+) expression vector (Novagen, Madison, WI) containing the thioredoxin-His-Tag sequence was digested with BamHI (GGATCC) and XhoI and gel extracted using the QIAquick gel extraction kit from QIAGEN (Chatsworth, CA). The BglII-XhoI DNA fragments were ligated to the BamHI-XhoI pET-32c(+) vector to create the coding sequence for thioredoxin-His-Tag-BVH-3 or thioredoxin-His-Tag-BVH-28 fusion protein. The ligated products were transformed into *E. coli* strain DH5a [f80 lacZ DM15 endA1 recA1 hsdR17 (^rK⁻K⁺) supE44 thi-11⁻ gyrA96 relA1 D(lacZYA-argF)U169] (Gibco BRL, Gaithersburg, MD) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). Recombinant pET-32c(+) plasmids were purified using a QIAGEN kit (Chatsworth, CA) and the nucleotide sequences at the fusion sites of thioredoxin-His-Tag and DNA insert were verified by DNA sequencing (Taq Dye Deoxy Terminator Cycle Sequencing kit, ABI, Foster City, CA).

EXAMPLE 2

This example illustrates the cloning of S. pneumoniae
5 protein genes in CMV plasmid pCMV-GH.

The DNA coding region of a S. pneumoniae protein was
inserted in phase downstream of a human growth hormone (hGH)
gene which was under the transcriptional control of the
10 cytomegalavirus (CMV) promotor in the plasmid vector pCMV-GH
(Tang et al., Nature, 1992, 356 :152). The CMV promotor is
non functional plasmid in E. coli cells but active upon
administration of the plasmid in eukaryotic cells. The
vector also incorporated the ampicillin resistance gene.

15 The coding region of BVH-3 gene (SEQ ID NO: 1) and BVH-28
gene (SEQ ID NO: 5) were obtained from rpSL301 (see example
1) using restriction enzymes BglII (AGATCT) and XbaI
(TCTAGA). The digested products were purified from agarose
20 gel using the QIAquick gel extraction kit from QIAgen
(Chatsworth, CA). The pCMV-GH vector (Laboratory of Dr.
Stephen A. Johnston, Department of Biochemistry, The
University of Texas, Dallas, Texas) containing the human
growth hormone to create fusion proteins was digested with
25 BglII and XbaI and purified from agarose gel using the
QIAquick gel extraction kit from QIAgen (Chatsworth, CA).
The BglII-XbaI DNA fragments were ligated to the BglII-XbaI
pCMV-GH vector to create the hGH-BVH-3 or hGH-BVH-28 fusion
protein under the control of the CMV promoter. The ligated
30 products were transformed into E. coli strain DH5a[f80 lacZ
DM15 endA1 recA1 hsdR17 (^rK⁻^mK⁺) supE44 thi-11⁻ gyrA96 relA1
D(lacZYA-argF)U169] (Gibco BRL, Gaithersburg, MD) according

to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). The recombinant pCMV plasmids were purified using a QIAgen kit (QIAgen, Chatsworth, CA).

5

The coding region of BVH-11 gene (**SEQ ID NO: 3**) was amplified by PCR (DNA Thermal Cyclor GeneAmp PCR system 2400 Perkin Elmer, San Jose, CA) from genomic DNA of serogroup 6 S. pneumoniae strain SP64 using the oligos that contained
10 base extensions for the addition of restriction sites BglII (AGATCT) and HindIII (AAGCTT). The PCR product was purified from agarose gel using a QIAquick gel extraction kit from QIAgen (Chatsworth, CA), digested with restriction enzymes (Pharmacia Canada Inc, Baie d'Urfe, Canada), extracted with
15 phenol : chloroform and precipitated with ethanol. The pCMV-GH vector (Laboratory of Dr. Stephen A. Johnston, Department of Biochemistry, The University of Texas, Dallas, Texas) was digested with BglII and HindIII and purified from agarose gel using the QIAquick gel extraction kit from
20 QIAgen (Chatsworth, CA). The BglII-HindIII DNA fragment was ligated to the BglII-HindIII pCMV-GH vector to create the hGH-BVH-11 fusion protein under the control of the CMV promoter. The ligated products were transformed into E. coli strain DH5a[f80 lacZ DM15 endA1 recA1 hsdR17 (⁺K⁻M⁺) supE44
25 thi-11⁻ gyrA96 relA1 D(lacZYA-argF)U169] (Gibco BRL, Gaithersburg, MD) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). The recombinant pCMV plasmid was purified using a QIAgen kit (Chatsworth, CA) and the nucleotide sequence of
30 the DNA insert was verified by DNA sequencing.

EXAMPLE 3

This example illustrates the use of DNA to elicit an immune response to S. pneumoniae antigens.

- 5
- A group of 8 female BALB/c mice (Charles River, St-Constant, Québec, Canada) were immunized by intramuscular injection of 50 µl three times at two- or three-week intervals with 100 µg of recombinant pCMV-GH encoding the BVH-3, BVH-11 or the
- 10 BVH-28 gene in presence of 50 µg of granulocyte-macrophage colony-stimulating factor (GM-CSF)- expressing plasmid pCMV-GH-GM-CSF (Laboratory of Dr. Stephen A. Johnston, Department of Biochemistry, The University of Texas, Dallas, Texas).
- As control, a group of mice were injected with 100 µg of
- 15 pCMV-GH in presence of 50 µg of pCMV-GH-GM-CSF. Blood samples were collected from the orbital prior to each immunization and seven days following the third injection and serum antibody responses were determined by ELISA using thioredoxin-His-Tag-S. pneumoniae fusion protein as coating
- 20 antigen. DNA immunization with recombinant plasmid pCMV-GH encoding the BVH-3, BVH-11 or the BVH-28 S. pneumoniae protein induced antibody reactive against the respective recombinant protein. The reciprocal antibody titers, defined as the highest serum dilution at which the absorbance values
- 25 were 0.1 above the background values, were above 4×10^3 .

EXAMPLE 4

- 30 This example illustrates the production and purification of recombinant S. pneumoniae proteins.

The recombinant pET plasmids containing the BVH-3, BVH-11 or the BVH-28 gene corresponding to the SEQ ID NO: 1, SEQ ID NO: 3 or the SEQ ID NO: 5 respectively were transformed by electroporation (Gene Pulser II apparatus, BIO-RAD Labs, Mississauga, Canada) into E. coli strain AD494 (DE3) (Dara⁻ leu7697 DlacX74 DphoA PvuII phoR DmalF3 F' [lac⁺(lacI^q) pro] trxB::Kan) (Novagen, Madison, WI). In this strain of E. coli, the T7 promotor controlling expression of the fusion protein is specifically recognized by the T7 RNA polymerase (present on the lDE3 prophage) whose gene is under the control of the lac promotor which is inducible by isopropyl-β-d-thio-galactopyranoside (IPTG). The transformant AD494(DE3)/rpET was grown at 37°C with agitation at 250 rpm in LB broth (peptone 10g/L, yeast extract 5g/L, NaCl 10g/L) containing 100μg of ampicillin (Sigma-Aldrich Canada Ltd., Oakville, Canada) per ml until the A₆₀₀ reached a value of 0.6. In order to induce the production of the thioredoxin-His·Tag-BVH-3, thioredoxin-His·Tag-BVH-11 or thioredoxin-His·Tag-BVH-28 fusion protein, the cells were incubated for 2 additional hours in the presence of IPTG at a final concentration of 1 mM. Induced cells from a 100 ml culture were pelleted by centrifugation and frozen at -70°C.

The purification of the fusion proteins from the soluble cytoplasmic fraction of IPTG-induced AD494(DE3)/rpET was done by affinity chromatography based on the properties of the His·Tag sequence (6 consecutive histidine residues) to bind to divalent cations (Ni²⁺) immobilized on the His·Bind metal chelation resin. Briefly, the pelleted cells obtained from a 100mL culture induced with IPTG were resuspended in

phosphate-buffered (PBS):500mM NaCl pH7.1, sonicated and spun at 20,000 X g for 20 min to remove debris. The supernatant was filtered (0.22µm pore size membrane) and deposited on a HiTrap® 1mL chelating pre-packed ready-to-use column (Pharmacia Biotech, Baie d'Urfé, Canada). The thioredoxin-His-Tag-S. pneumoniae fusion protein was eluted with 1M imidazole-500mM NaCl-PBS pH7.1. The removal of the salt and imidazole from the sample was done by dialysis against PBS at 4°C. The quantities of fusion protein obtained from the soluble fraction of E. coli was estimated by MicroBCA (Pierce, Rockford, Illinois).

EXAMPLE 5

15

This example illustrates the protection of mice against fatal pneumococcal infection by immunization.

Groups of 8 female BALB/c mice (Charles River) were immunized subcutaneously three times at three-week intervals with either 25 µg of affinity purified thioredoxin-His-Tag-BVH-3 fusion protein in presence of 15 µg of QuilA adjuvant (Cedarlane Laboratories Ltd, Hornby, Canada) or, as control, with QuilA adjuvant alone in PBS. Blood samples were collected from the orbital sinus on day 1, 22 and 43 prior to each immunization and seven days (day 50) following the third injection. One week later the mice were challenged with approximately 10⁶ CFU of the type 3 S. pneumoniae strain WU2. Samples of the S. pneumoniae challenge inoculum were plated on chocolate agar plates to determine the CFU and to verify the challenge dose. Deaths were recorded for

a period of 14 days and on day 14 post-challenge, the surviving mice were sacrificed and blood samples tested for the presence of S. pneumoniae organisms. The survival data are shown in table 1.

5

Prechallenge sera were analyzed for the presence of antibodies reactive with S. pneumoniae by standard immunoassays. Elisa and immunoblot analyses indicated that immunization with recombinant S. pneumoniae protein produced in E. coli elicited antibodies reactive with both, recombinant and native pneumococcal protein.

10

Table 1. Protection mediated by recombinant BVH-3 protein

Immunogen	No. of mice alive : no. of mice dead 14 days post-challenge	Median day of death
BVH-3	8 : 0	>14
none	0 : 8	1

15

All mice immunized with BVH-3 recombinant protein survived to infection while none of the control mice given adjuvant alone survived. There was a significant difference in survival between the two groups of mice ($P < 0.0001$, log rank test for nonparametric analysis of survival curves; $P = 0.0002$, Fisher's exact test). All hemocultures from surviving mice were negative at day 14 post-challenge.

20

25

EXAMPLE 6

This example describes the cloning of BVH-3 and BVH-11 genes from a variety of S. pneumoniae strains and the molecular conservation of these genes.

- 5 Molecular analysis of chromosomal DNA from various S. pneumoniae isolates with DNA probes spanning different regions of BVH-3 or BVH-11 revealed the presence of one BVH-3 gene copy and two BVH-11 gene copies. The two BVH-11 gene copies are not identical and the genes were
- 10 arbitrarily designated BVH-11 (SEQ ID NO:12; ORF at nucleotides 45 to 2567) and BVH-11-2 (SEQ ID NO:13; ORF at nucleotides 114 to 2630).

- The first amino acids of the BVH-3 and BVH-11 coding
- 15 regions have the characteristics of leader sequences also known as signal peptides. The consensus signal peptidase cleavage site L-X-X-C of lipoprotein modification/processing sites was present in the sequences. Mature BVH-3, BVH-11 and BVH-11-2 proteins from S. pneumoniae SP64 have 1019, 821 and 819 amino acids,
- 20 respectively. The regions of S. pneumoniae genes coding for mature BVH-3, termed BVH-3M, (nucleotides 1837 - 4896; SEQ. ID. NO: 11), BVH-11M (nucleotides 102-2567; SEQ. ID. NO: 12) and BVH-11-2M (nucleotides 171-2630; SEQ. ID. NO:
- 25 13), were amplified by PCR (DNA Thermal Cycler GeneAmp PCR system 2400 Perkin Elmer, San Jose, CA) from genomic DNA of 6 or 7 S. pneumoniae strains. Serogroup 6 S. pneumoniae SP64 and serogroup 9 SP63 clinical isolates were provided by the laboratoire de la santé publique du Québec, Sainte-
- 30 Anne-de-Bellevue; serotype 4 strain JNR.7/87 was provided by Andrew Camilli, Tufts University School of Medicine, Boston; Rx1 strain, a nonencapsulated derivative of the type 2 strain D39 and the type 3 strains A66 and WU2 were provided by David E. Briles from University of Alabama,
- 35 Birmingham and the type 3 clinical isolate P4241 was provided by the centre de recherche en infectiologie du

centre hospitalier de l'université Laval, Sainte-Foy. The sets of oligonucleotide primers OCRR479-OCRR480; HAMJ160-OCRR488 and HAMJ160-HAMJ186, that contained base extensions for the addition of restriction sites were used for the amplification of BVH-3, BVH-11 and BVH-11-2 gene, respectively, with the exception of BVH-11 gene from SP64 strain which was amplified using the set of primers consisting of HAMJ487 and OCRR488. Primer sequences are listed below (Table 2). PCR products were purified from agarose gel using a QIAquick gel extraction kit from QIAGEN (Chatsworth, CA) and digested BglII-XbaI or BglII-HindIII (Pharmacia Canada Inc, Baie d'Urfé, Canada). Digestions were cleaned using a QIAquick PCR purification kit from QIAGEN (Chatsworth, CA). The PCR products were ligated to the BglII-XbaI or BglII-HindIII pSL301 vector. The ligated products were transformed into E. coli strain DH5 α [ϕ 80 lacZ Δ M15 endA1 recA1 hsdR17 ('K'K') supE44 thi-1 λ gyrA96 relA1 Δ (lacZYA-argF)U169] (Gibco BRL, Gaithersburg, MD) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). Recombinant pSL301 plasmids (rpSL301) containing BVH-3, BVH-11 or BVH11-2 were purified using a QIAGEN kit (Chatsworth, CA) and DNA inserts were sequenced (Taq Dye Deoxy Terminator Cycle Sequencing kit, ABI, Foster City, CA). The figures 11 and 12 depict the consensus sequence established from the BVH-3, and BVH-11 deduced amino acid sequences, respectively. Comparison of BVH-3 protein sequences revealed 99 to 100% identity of sequences for all strains with the exception that BVH-3 from serogroup 9 SP63 strain (SEQ. ID. NO: 15 and SEQ. ID. NO: 16) misses a stretch of 177 amino acids corresponding to residues 244 to 420 on BVH-3'protein sequence of S. pneumoniae SP64. Analysis of sequences of additional serogroup 9 strains revealed BVH-3 molecule having the same deletion in 3 out of 4 strains

thus suggesting that the 3 strains are members of a S. pneumoniae serogroup 9 clone.

Comparison of 13 BVH-11 nucleotide sequences obtained from
5 7 S. pneumoniae strains, revealed that the nucleotide
sequences are very similar. Computer analysis (MacVector,
Clustal W 1.4) using multiple alignment of the predicted
BVH-11 protein sequences revealed that these sequences were
75% identical and 82 % homologous on a length of 834 amino
10 acids. Pairwise alignment revealed 80 to 100% identity
(Figure 13). The sequences showed great similarity in
overall organization. Variability in the primary sequence
of these proteins is almost restricted to the last 125
amino acids in the C-terminal portion of the proteins. This
15 region constitutes a domain. Close examination of this
domain revealed two groups of sequences. The first 9
sequences from the figure 13 belong to one group while the
last 4 sequences belong to another group. A 39% identity
value is obtained when the domain sequences of the 13
20 proteins are compared (MacVector, Clustal W 1.4). The
identity value increased to more than 92% when sequences
belonging to a same group are compared.

25 EXAMPLE 7

This example illustrates the homology of portions of BVH-3
and BVH-11 genes.

30 Molecular analysis with DNA probes derived from BVH-3 and
BVH-11 genes indicated that BVH-3 and BVH-11 were related.
In dot blot hybridization studies, DNA probe consisting of
either, BVH-3 or BVH-11, gene sequence hybridized to both,
BVH-3 and BVH-11 genes thus indicating that BVH-3 and BVH-
35 11 genes shared homologous sequences. Comparison of
sequences revealed that the ORFs and the proteins were 43

and 33% identical, respectively. Closer examination revealed that the region corresponding to amino acids 1 to 225 in BVH-3 and 1 to 228 in BVH-11 were 73 and 75% identical at the DNA and protein level, respectively. In contrast, the 3' regions corresponding to amino acids 226 to 1039 from BVH-3 and amino acids 229-840 from BVH-11 were only 34 and 22% identical at the DNA and protein level, respectively. Thus the 5' termini of BVH-3 and BVH-11 genes appear to contain highly conserved sequences while the remaining parts of the genes are highly divergent. These results suggest that BVH-3 and BVH-11 might share similar functions mediated by sequences present in the conserved region whereas BVH-3- and BVH-11-specific functions might be mediated by sequences in the divergent region.

EXAMPLE 8

This example describes the cloning of truncated BVH-3, BVH-11 and BVH-11-2 genes by polymerase chain reaction (PCR) and the expression of truncated BVH-3 and BVH-11 molecules.

Gene fragments were amplified by PCR using pairs of oligonucleotide engineered to amplify fragments spanning the BVH-3 (SEQ ID NO: 1 and SEQ ID NO: 11), BVH-11 (SEQ ID NO: 3 and SEQ ID NO: 12) or BVH-11-2 (SEQ ID NO: 13) gene from S. pneumoniae strain SP64. Each of the primers had a restriction endonuclease site at the 5' end, thereby allowing directional in-frame cloning of the amplified product into the digested plasmid vector (Tables 2 and 3). PCR-amplified products were digested with restriction endonucleases and ligated to either linearized plasmid pSL301 (see example 1), pCMV-GH (see example 2) or pET (Novagen, Madison, WI) expression vector digested likewise or digested with enzymes that produce compatible cohesive

ends. Recombinant pSL301 and recombinant pCMV-GH plasmids were digested with restriction enzymes for the in-frame cloning in pET expression vector. Clones were first stabilized in E. coli DH5 α before introduction into E. coli BL21(λ DE3) or AD494 (λ DE3) for expression of truncated BVH-3 or BVH-11 molecules. Each of the resultant plasmid constructs was confirmed by nucleotide sequence analysis. The recombinant proteins were expressed as N-terminal fusions with the thioredoxin and His-tag or as C-terminal fusions with an His-tag. The expressed recombinant proteins were purified from supernatant fractions obtained from centrifugation of sonicated IPTG-induced E. coli cultures using a His-Bind metal chelation resin (QIAgen, Chatsworth, CA). The gene products generated are listed in the table 3. The gene products corresponding to the N-terminal region including the signal sequence are designated as Lipidated-proteins or lipoproteins (L-proteins). The gene products corresponding to the N-terminal region lacking the signal sequence are identified as protein without signal sequence (w/o ss).

Table 2. List of PCR oligonucleotide primers

Primer	SEQ. ID.	Sequence 5' - 3'	Nucleotide position	Restriction sites
OCRR 479	17	cagtagatctgtgacctatgcactaaac	SEQ ID 1 :61-78	BglII
OCRR 480	18	gatctctagactactgctattccttacgctatg	SEQ ID 11 :4909-4887	XbaI
OCRR 497	19	atcactcgagcattacctggataatcctgt	SEQ ID 1 :1525-1506	XhoI
OCRR 498	20	ctgctaagcttatgaaagatttagat	SEQ ID 1 :1534-1548	HindIII

OCRR 499	21	gatactcgagctgctattccttac	SEQ ID 11 :4906-4893	XhoI
HAMJ 172	22	gaatctcgagttaagctgctgctaattc	SEQ ID 1 : 675-661	XhoI
HAMJ 247	23	gacgctcgagcgctatgaaatcagataaattc	SEQ ID 1 :3117-3096	XhoI
HAMJ 248	24	gacgctcgaggcgattacctggataatcctgttcacg	SEQ ID 1 :1527-1501	XhoI
HAMJ 249	25	cagtagatctcttcacatttattgaaaagagg	SEQ ID 11 : 1749-1771	BglII
HAMJ 278	26	ttatttctccatatggacttgacagaagagcaaattaag	SEQ ID 1 :1414-1437	NdeI
HAMJ 279	27	cgccaagcttcgctatgaaatcagataaattc	SEQ ID 1 :3117-3096	HindIII
HAMJ 280	28	cgccaagctttccacaataataagtcgattgatt	SEQ ID 1 :2400-2377	HindIII
HAMJ 281	29	ttatttctccatatggaagtacatcttgaaaaagaa	SEQ ID 1 :2398-2421	NdeI
HAMJ 300	30	ttatttctccatatggcgctatgcactaaaccagc	SEQ ID 1 :62-82	NdeI
HAMJ 313	31	ataagaatcgggcgcttcacaataataagtcgattgatt	SEQ ID 1 :2400-2377	NotI
OCRR 487	32	cagtagatctgtgcttatgaactagggttgc	SEQ ID 3 :58-79	BglII
OCRR 488	33	gatcaagcttgctgctacctttacttactctc	SEQ ID 12 :2577-2556	HindIII
HAMJ 171	34	ctgagatatccgttatcggtcaaac	SEQ ID 3 :1060-1075	EcoRV
HAMJ 251	35	ctgcaagcttttaaagggaataataacg	SEQ ID 3 :1059-1045	HindIII
HAMJ 264	36	cagtagatctgcagaagccttcctatctg	SEQ ID 3 :682-700	BglII
HAMJ 282	37	tcgccaagcttcgttatcggtcaaacattggg	SEQ ID 3 :1060-1081	HindIII
HAMJ 283	38	ataagaatcgggcgcttactctccttaataaagccaat agtt	SEQ ID 3 :2520-2492	NdeI
HAMJ 284	39	catgccatggacattgatagctcttgaaacagc	SEQ ID 3 :856-880	NcoI
HAMJ 285	40	cgccaagcttcttactctccttaataaagccaatag	SEQ ID 3 :2520-2494	HindIII
HAMJ 286	41	cgacaagcttaacatggctgctagcggtacc	SEQ ID 3 :2139-2119	HindIII
HAMJ 287	42	cataccatgggcctttatgaggcacctaag	SEQ ID 3 :2014-2034	NcoI
HAMJ 288	43	cgacaagcttaagtaaatcttcagcctctctcag	SEQ ID 3 :2376-2353	HindIII

HAMJ 289	44	gataccatggctagcgaccatgttcaaagaa	SEQ ID 3 :2125-2146	NcoI
HAMJ 290	45	cgccaagcttatcatccacttaacttgactttatcac	SEQ ID 3 :1533-1508	HindIII
HAMJ 291	46	cataccatggatattcttgccttcttagctccg	SEQ ID 3 :1531-1554	NcoI
HAMJ 301	47	catgccatgggtgcttatgaactagggtttgc	SEQ ID 3 :59- 79	NcoI
HAMJ 302	48	cgccaagctttagcgttacaaaaccattatc	SEQ ID 3 :2128-2107	HindIII
HAMJ 160	49	gtattagatctgttcctatgaacttggctgcacca	SEQ ID 13 : 172-196	BglII
HAMJ 186	50	cgcccttagactactgtataggagccgg	SEQ ID 13: 2460-2443	XbaI
HAMJ 292	51	catgccatggaaaacatttcaagcctttacgtg	SEQ ID 11: 754-778	NcoI
HAMJ 293	52	cgacaagcttctgtataggagccggttgacttgc	SEQ ID 11 : 2457-2434	HindIII
HAMJ 294	53	catgccatgggttcgtaaaaataaggcagaccaag	SEQ ID 11 : 2038-2062	NcoI
HAMJ 297	54	catgccatggaagcctattggaatgggaag	SEQ ID 11 : 622-642	NcoI

Table 3. Lists of truncated BVH-3 and BVH-11 gene products generated from S. pneumoniae SP64

PCR-primer sets	Protein designation	Identification (encoded amino acids)	SEQ. ID.No.	Cloning vector
OCRR479-OCRR480	BVH-3M	BVH-3 w/o ss (21-1039)	55	pSL301
OCRR479-OCRR497	BVH-3AD	BVH-3 N'end w/o ss (21-509)	56	pSL301
HAMJ248-HAMJ249	L-BVH-3AD	BVH-3 N'end (1-509)	57	pET-21(+)
OCRR498-OCRR499	BVH-3B	BVH-3 C'end (512-1039)	10	pSL301
OCRR479-HAMJ172	BVH-3C	BVH-3 N'end w/o ss (21-225)	59	pET-32 c(+)
OCRR487-OCRR488	BVH-11M	BVH-11 w/o ss (20-840)	60	pCMV-GH
HAMJ251-OCRR487	BVH-11A	BVH-11 N'end w/o ss (20-353)	61	pET-32 c(+)
HAMJ171-OCRR488	BVH-11B	BVH-11 C'end (354-840)	62	pET-32 a(+)
HAMJ264-OCRR488	BVH-11C	BVH-11 C'end (228-840)	63	pET-32 a(+)
HAMJ278-HAMJ279	NEW1	BVH-3 C'end (472-1039)	64	pET-21b(+)
HAMJ278-HAMJ280	NEW2	BVH-3 C'end (472-800)	65	pET-21b(+)
HAMJ281-HAMJ279	NEW3	BVH-3 C'end (800-1039)	66	pET-21b(+)
HAMJ284-HAMJ285	NEW4	BVH-11 C'end (286-840)	67	pET-21d(+)
HAMJ284-HAMJ286	NEW5	BVH-11 internal (286-713)	68	pET-21d(+)
HAMJ287-HAMJ288	NEW6	BVH-11 internal (672-792)	69	pET-21d(+)
HAMJ285-HAMJ289	NEW7	BVH-11 internal (709-840)	70	pET-21d(+)
HAMJ284-HAMJ290	NEW8	BVH-11 internal (286-511)	71	pET-21d(+)

HAMJ286-HAMJ291	NEW9	BVH-11 internal (511-713)	72	pET-21d(+)
HAMJ160-HAMJ186	BVH-11-2M	BVH-11-2 w/o ss (20-838)	73	pSL301
HAMJ292-HAMJ293	NEW10	BVH-11-2 C'end (271-838)	74	pET-21d(+)
HAMJ293-HAMJ294	NEW11	BVH-11-2 C'end (699-838)	75	pET-21d(+)
HAMJ282-HAMJ283	BVH-11B	BVH-11 C'end (354-840)	62	pET-21b(+)
HAMJ286-HAMJ297	NEW14	BVH-11-2 internal (227-699)	77	pET-21d(+)
HAMJ300-HAMJ313	NEW15	BVH-3 N'end w/o ss (21-800)	78	pET-21b(+)
HAMJ301-HAMJ302	NEW16	BVH-11 N'end w/o ss (20-709)	79	pET-21d(+)

EXAMPLE 9

This example describes the isolation of monoclonal antibodies (Mabs) and the use of Mabs to characterize BVH-3, BVH-11 and BVH-11-2 protein epitopes.

Female BALB/c mice (Charles River) were immunized subcutaneously with BVH-3, BVH-11 or BVH-11-2 gene products from S. pneumoniae strain SP64 in presence of 15 µg of QuilA adjuvant (Cedarlane Laboratories Ltd, Hornby, Canada). One set of mice (fusion experiment 1) were immunized on day 1 and 14 with 25 µg of affinity purified thioredoxin-His•Tag-BVH-3M fusion protein. A second group of mice (fusion experiment 2) were immunized three times at three-week intervals with 25 µg of affinity purified thioredoxin-His•Tag-BVH-11M. A third group of mice (fusion experiment 3) were immunized on day 1 and day 15 with 25 µg of affinity purified thioredoxin-His•Tag-BVH-11-2M fusion protein. A fourth group of mice (fusion experiment 4) were immunized on day 1 with 25 µg of affinity purified thioredoxin-His•BVH-11B fusion protein and boosted by intravenous injection on day 16 and on day 37 with recombinant BVH-11B in PBS. Three to four days before fusion, mice were injected intravenously with 25 µg of the respective antigen suspended in PBS alone. Hybridomas were produced by fusion of spleen cells with nonsecreting SP2/0 myeloma cells as previously described by J. Hamel et al. [J. Med. Microbiol., 23, pp163-170 (1987)]. Culture supernatants of hybridomas were initially screened by enzyme-linked-immunoassay according to the procedure described by Hamel et al. (Supra) using plates coated with preparations of purified recombinant proteins or suspensions of heat-killed S. pneumoniae cells. Positive hybridomas selected on the basis of ELISA reactivity with a

variety of antigens were then cloned by limiting dilutions, expanded and frozen.

Hybridomas were tested by ELISA or Western immunoblotting against BVH-3 and BVH-11 gene products in order to characterize the epitopes recognized by the Mabs. BVH-3 and BVH-11 shared common epitopes with 6 Mabs (H3-1-F9, H3-1-D4, H3-1-H12, H11-1-E7, H11-1-H10 and H11-1.1-G11) showing reactivities with both proteins (Table 4). BVH-11 and BVH-11-2 molecules from S. pneumoniae SP64 shared common epitopes not present on BVH-3 with Mabs (3A1, 13C11, 10H10, 1D8, 10G9, 10A2, 3E8, 10D7, 2H7 and 6H7) reactive with both, BVH-11 and BVH-11-2, recombinant proteins (Table 5).

15

Table 4. Reactivity of BVH-3-immunoreactive Mabs with a panel of BVH-3 and BVH-11 gene products

Mabs	a. Immunoreactivity with						
	BVH-3M 21-1039	BVH-3A 21-509	BVH-3B 512-1039	BVH-3C 21-225	NEW2 472-800	NEW3 800-1039	BVH-11M 20-840
H3-1-F9	+	+	-	+	-	-	+
H3-1-D4	+	+	-	+	-	-	+
H3-1-H12	+	+	-	+	-	-	+
H3-2-G2	+	+	-	-	-	-	-
H3-3-A1	+	+	-	-	-	-	-
H3-4-D3	+	-	+	-	-	+	-
H11-1-E7	+	+	-	+	-	-	+
H11-1-H10	+	+	-	+	-	-	+
H11-1.1-G11	+	+	-	+	+	-	+

Table 5. Reactivity of Mabs raised against BVH-11-2 protein from S. pneumoniae strain SP64 with a panel of BVH-11 gene products

Mabs ^a	b. Immunoreactivity with							
	c. BVH-11 products				d. BVH-11-2 products			
	BVH-11M 20-840	NEW8 286-511	NEW9 511-713	BVH-11B 354-840	BVH-11-2 20-838	NEW10 271-838	NEW11 699-838	NEW14 227-699
3A1	+	+	-	+	+	+	-	+
13C1	+	+	+	+	+	+	-	+
10H10	+	+	+	+	+	+	-	+
1D8	+	+	-	+	+	+	-	+
10G9	+	-	-	+	+	+	-	+
10A2	+	-	-	+	+	+	-	+
3E8	+	-	-	+	+	+	-	+
10D7	+	-	-	+	+	+	-	+
2H7	+	-	-	-	+	-	-	-
6H7	+	-	-	-	+	-	-	-
3A4	-	-	-	-	+	+	+	-
14H6	-	-	-	-	+	+	+	-
7G2	-	-	-	-	+	+	-	+
13H10	-	-	-	-	+	-	-	+
7E8	-	-	-	-	+	-	-	-
7H6	-	-	-	-	+	-	-	-

^a Mabs listed in this table were not reactive with recombinant BVH-3 molecule

5

The results obtained from the immunoreactivity studies of the Mabs (Table 4 and Table 5) are in agreement with the protein sequences derived from the respective gene sequences. Indeed the Mabs cross-reactive with BVH-3 and
 10 BVH-11 molecules recognized BVH-3C protein corresponding to

This example illustrates the simultaneous expression of BVH-3 and BVH-11 gene products by S. pneumoniae.

5 A standard Western blot technique was used to investigate whether BVH-3 and BVH-11 genes were expressed in S. pneumoniae. S. pneumoniae strain SP64 and SP63 were grown overnight at 37°C in 5% CO₂ on chocolate agar plates, bacteria were suspended in PBS and heat-killed at 56°C for 20 min. For the preparation of antigens, suspensions of S. pneumoniae were treated with sample buffer containing SDS and 2-mercaptoethanol for 5 min at 100°C. Pneumococcal protein antigens were resolved by SDS-PAGE electrophoresis according to the method of Laemmli [Nature, 227, pp. 680-685 (1970)]. After SDS-PAGE, the proteins were transferred electrophoretically from the gel to nitrocellulose paper by the method of Towbin [Proc. Natl. Acad. Sci. USA, 76, pp. 4350-4354 (1979)] and probed with mouse antiserum or monoclonal antibodies. The detection of antigens reactive with the antibodies was performed by indirect enzyme-immunoassay using conjugated-anti-mouse immunoglobulins and a colour substrate. When antiserum raised to recombinant BVH-3 was tested against S. pneumoniae SP64 antigens, two reactive bands having apparent molecular masses of 127 kDa and 99 kDa were detected. Bands having the same apparent molecular masses were also detected when Mabs H3-1-F9, H3-1-D4, H3-1-H12, H11-1-E7, H11-1-H10 and H11-1.1-G11 were used individually as immunological probes. In contrast, Mabs specific for the BVH-3 molecule detected the 127 kDa band only and Mabs specific for BVH-11 detected the 99 kDa band only thus confirming the identity of the 127 and 99 kDa bands as BVH-3 and BVH-11, respectively. These studies provide evidence that BVH-3 and BVH-11 proteins are simultaneously present on S. pneumoniae. Moreover, the results are consistent with our previous observations that BVH-3 and BVH-11 possess epitopes that are common to both proteins and epitopes that are exclusive to either protein.

In S. pneumoniae SP64, mature BVH-3, BVH-11 and BVH-11-2 are proteins of 1019, 821 and 819 amino acids with predicted molecular mass of 112.5 kDa, 92.4 kDa, and 91.7 kDa, respectively. Although there is a discrepancy between the molecular mass predicted from the sequence and the molecular mass calculated on SDS-PAGE, BVH-3 can be distinguished from BVH-11 by its higher molecular mass. Moreover, BVH-3 molecules from S. pneumoniae strain SP63 have an apparent molecular mass of 112 kDa in SDS-PAGE compared to 127 kDa for BVH-3 of SP64 strain. This data is consistent with the deletion of a stretch of 177 amino acid residues in BVH-3 of S. pneumoniae strain SP63.

15

EXAMPLE 11

This example describes the protection conferred in experimental infection of mice vaccinated with recombinant BVH-3 or BVH-11 gene products.

Groups of 7 or 8 female BALB/c mice (Charles River) were immunized subcutaneously three times at three-week intervals with either affinity purified thioresdoxin-His•Tag-BVH-3M fusion protein, affinity purified thioresdoxin-His•Tag-BVH-11M fusion protein or, as control, with QuilA adjuvant alone in PBS. Twelve to 14 days following the third immunization, the mice were challenged intravenously with S. pneumoniae WU2 strain or intranasally with P4241 strain. Samples of the S. pneumoniae challenge inoculum were plated on chocolate agar plates to determine the CFU and to verify the challenge dose. The challenge dose was approximately 10^6 CFU. Deaths were recorded for a period of 14 days and on day 14 post-challenge, the surviving mice were sacrificed and blood samples tested for

the presence of S. pneumoniae organisms. The survival data are shown in Tables 6 and 7.

5

Table 6. Protection mediated by recombinant BVH-3M and BVH-11M proteins in experimental infection with virulent S. pneumoniae WU2

Experiment	Immunogen	Alive : dead*	Median days alive
1	BVH-3M	8 : 0	>14
	none	0 : 8	1
2	BVH-11M	8 : 0	>14
	none	0 : 8	1

10 * The number of mice alive : the number of mice dead on day 14 post-challenge.

Table 7. Protection mediated by recombinant BVH-3M and BVH-11M proteins in experimental pneumonia with virulent S. pneumoniae P4241

15

Experiment	Immunogen	Alive : dead*	Median day alive
1	BVH-3M	6 : 1	>14
	none	1 : 7	4.5
2	BVH-3M	8 : 0	>14
	BVH-11M	8 : 0	>14
	none	0 : 8	4

* The number of mice alive : the number of mice dead on day 14 post-challenge.

20 All mice immunized with recombinant BVH-3M or BVH-11M protein survived to infection with WU2 while none of the control mice given adjuvant alone survived. All except one mice immunized with recombinant BVH-3M or BVH-11M protein survived to infection with P4241 while only one control mice given adjuvant alone survived. All hemocultures from

surviving mice were negative at day 14 post-challenge. These results clearly indicate that both, BVH-3M and BVH-11M, elicit protective anti-pneumococcal immune responses in mice. The fact that these proteins are highly conserved among S. pneumoniae isolates emphasize the potential of BVH-3 and BVH-11 as universal vaccine candidates. Indeed, the BVH-3 and BVH-11 proteins from serogroup 6 S. pneumoniae strain SP64 elicited protection against pneumococcal infections with strains of different capsular serotypes.

Ideally, a vaccine that could protect against pneumococcal disease, could protect against meningitis, otitis media, bacteremia and pneumonia. BVH-3 and BVH-11 were protective against lethal systemic- and pneumonia-infection models thus suggesting that, in humans, BVH-3- and BVH11-protein-based vaccines could reduce the incidence of a wide spectrum of disease caused by virtually all S. pneumoniae independently of the capsular serotype.

Data from Tables 6 and 7 clearly demonstrate that BVH-3 and BVH-11 were, both, protection-eliciting molecules of S. pneumoniae. It was not known, however, whether protection can be mediated by specific sequences that were not shared on BVH-3 and BVH-11 molecules. Groups of female BALB/c mice (Charles River) were immunized subcutaneously three times at three-week intervals with either affinity purified thioredoxin-His•Tag- BVH-3AD, -BVH-3B or -BVH-3C fusion protein in presence of 15 µg of QuilA adjuvant (Cedarlane Laboratories Ltd, Hornby, Canada). Control mice were immunized with QuilA adjuvant alone in PBS or affinity purified thioredoxin-His•Tag or thioredoxin-His•Tag-fusion protein (His-Thio) in presence of QuilA.

To determine the protective ability of a set of truncated proteins, termed NEW4, NEW5, NEW6, NEW7, NEW8, NEW9, NEW10,

NEW11, NEW14 and BVH-11B, groups of female BALB/c mice (Charles River) were immunized subcutaneously two times at three-week intervals with 25 µg of either affinity purified His•Tag-fusion protein in presence of 15 µg of QuilA
5 adjuvant. Ten to 14 days following the last immunization, the mice were challenged with virulent S. pneumoniae. Our results indicate that, BVH-3B, a truncated BVH-3 molecule consisting of amino acids 512-1039, elicited protection against the mouse-virulent strains WU2 and P4241.
10 Similarly, BVH-11B, NEW4 and NEW5 molecules, three truncated BVH-11 molecules consisting of amino acids 354-840, amino acids 286-840 and amino acids 286-713, respectively, elicited protection against experiment intravenous challenge with WU2 and intranasal challenge
15 with P4241. Moreover, vaccination with NEW10 and NEW14, consisting of amino acids 272-838 and amino acids 227-699 from BVH-11-2 molecule also resulted in protection against death with the pneumococcal strains. These results indicate that the region comprising 428 amino acids
20 extending from amino acids 286-713 and amino acids 272-699 on S. pneumoniae SP64 BVH-11 and BVH-11-2 protein sequences, respectively, contains protective epitopes. This region is highly conserved with a global 91% identity and 94% homology among thirteen BVH-11 protein sequences.

25

Table 8. Evaluation of protection elicited by vaccination of mice with BVH-3 and BVH-11 gene products

Experiment	Immunogen	Challenge with WU2		Challenge with P4241	
		Alive : dead ^a	Median day alive	Alive : dead	Median day alive
1 ^b	None	0 : 8	1.5	1 : 7	4.5
	NEW4	8 : 0	>14	8 : 0	>14
	NEW5	8 : 0	>14	8 : 0	>14
	NEW7	0 : 8	2	0 : 8	5
	BVH-11M	8 : 0	>14	8 : 0	>14
2 ^b	None	0 : 8	1	0 : 8	4
	NEW5	8 : 0	>14	8 : 0	>14
	NEW8	0 : 8	1.5	0 : 8	5.5
	NEW9	3 : 5	3.5	2 : 6	7
	BVH-11M	8 : 0	>14	8 : 0	>14
3 ^b	None	0 : 8	1	0 : 8	4
	NEW6	0 : 8	1	4 : 4	10.5 ^c
	NEW10	8 : 0	>14	8 : 0	>14
	NEW11	0 : 8	1.5	1 : 7	6
	BVH-11M	8 : 0	>14	8 : 0	>14
4 ^b	None	0 : 8	2	0 : 8	4
	BVH-11B	7 : 1	>14	8 : 0	>14
	NEW14	8 : 0	>14	8 : 0	>14
5	His-Thio	0 : 8	2		
	BVH-3AD	1 : 7	2.5		
	BVH-3B	5 : 3	>14		
6	His-Thio	0 : 8	1		
	BVH-3C	0 : 8	1		

^a The number of mice alive : the number of mice dead on day 14 post-challenge.

5 ^b The WU2 challenge dose was 10⁵ CFU.

^c Mice living longer than 14 days were assigned a survival time of 14 days for the determination of median values.

EXAMPLE 12

This example described the cloning and expression of a
5 chimeric gene encoding for a chimeric polypeptide
corresponding to the carboxy-terminal region of BVH-3 in
fusion at the C' end to the carboxy-terminal region of BVH-
11 and the additive protection observed after vaccination
with a chimeric polypeptide.

10

It is clear from the studies described above that BVH-3 and
BVH-11 are serologically distinct molecules simultaneously
present on S. pneumoniae. The results of immunological
studies of mice indicate that both proteins are good
15 vaccine candidates. These proteins have the potential to
provide protection against all pneumococci, regardless of
serotype. Even though the two proteins share epitopes and
sequences, they have different characteristics and may
serve different biological functions. Thus, immunization
20 against the two proteins may provide a higher level of
protection than that imparted by each individually. To
examine this, several avenues where full-length or
truncated BVH-3 and BVH-11 are administered in combination
or in conjugation can be explored. Here we describe the
25 genetic engineering of a BVH-3-BVH-11 fusion gene and
protein, termed NEW12 (SEQ ID NO:76 and SEQ ID NO:58,
respectively), and the potential use of NEW12 protein as a
vaccine.

30 BVH-3 and BVH-11 gene fragments corresponding to the 3' end
of the genes were amplified by PCR using pairs of
oligonucleotides engineered to amplify fragments spanning
nucleotides 1414 to 3117 (SEQ ID NO: 1) and nucleotides 1060
to 2520 (SEQ ID NO: 3) from S. pneumoniae strain SP64 BVH-3
35 and BVH-11 genes, respectively. The primers used, HAMJ278
and HAMJ279; HAMJ282 and HAMJ283 had a restriction

endonuclease site at the 5' end, thereby allowing directional in-frame cloning of the amplified product into the digested pET21b(+) plasmid vector (Table 2). PCR-amplified products were digested with restriction
5 endonucleases and ligated to linearized plasmid pET21b(+) vector digested likewise. The resultant plasmid constructs were confirmed by nucleotide sequence analysis. The recombinant pET21b(+) plasmid containing the NdeI-HindIII BVH-3 PCR product was linearized by digestion with the
10 restriction enzymes HindIII and NotI for the in-frame cloning of the HindIII-NotI DNA fragment obtained from the recombinant pET21b(+) vector containing the BVH-11 gene fragment. Clones were first stabilized in E. coli DH5 α before introduction into E. coli BL21(λ DE3) for expression
15 of a chimeric pneumococcal protein molecule. The recombinant chimeric polypeptide, termed NEW 12, was expressed as C-terminal fusion with an His-tag. The expressed recombinant NEW 12 protein was purified from supernatant fractions obtained from centrifugation of
20 sonicated IPTG-induced E. coli cultures using a His-Bind metal chelation resin (QIAgen, Chatsworth, CA).

According to the same procedure described above, it is possible to construct other chimeric polypeptides, as a
25 result of a simultaneous expression of New 1 and New 4, New 1 and New 5, New 1 and New 10, or New 1 and New 14. The construction can be with New 1 upstream or downstream of New 4, New 5, New 10, BVH-11B or New 14. It is also possible to construct other chimeric polypeptides as a
30 result of a simultaneous expression of more than two fragments of either genes of BVH-3, BVH-11 or BVH-11-2.

Groups of 8 female BALB/c mice (Charles River) were immunized subcutaneously two times at three-week intervals
35 with 25 μ g of either affinity purified His-Tag-fusion NEW1,

BVH-11B or NEW12 protein in presence of 15 μ g of QuilA adjuvant. Ten to 14 days following the last immunization, the mice were challenged with virulent S. pneumoniae. As demonstrated before, NEW1 and BVH-11B molecules comprising amino acids 472 to 1039 from BVH-3 protein and amino acids 354-840 from BVH-11 protein, respectively, correspond to portions of the proteins capable of eliciting a protective immune response. To determine if a chimeric polypeptide would significantly improve the protection compared with those seen for the individual counterparts, the challenge dose was adjusted in a manner that protection was not expected with NEW1 and BVH-11B molecules. Interestingly, the chimeric NEW12 protein, elicited protection against the mouse-virulent strains WU2 and P4241. Seven out of 8 mice immunized with NEW12 were still alive 10 days after the challenge while 28 out of 32 mice immunized with NEW1, BVH-11B, BVH-3M or adjuvant alone were dead by five days post-challenge. Thus, vaccination of mice with NEW12 provided the highest degree of protection against WU2 challenge. These results indicate that immunization with a chimeric polypeptide and possibly a combination of BVH-3 and BVH-11 gene products can provide additional protection to that obtained by administration of BVH-3 or BVH-11 antigens alone.

Table 9. Evaluation of protection elicited by vaccination of mice with the chimeric NEW12 molecule

Immunogen	Challenge with WU2		Challenge with P4241	
	Alive : dead ^a	Median day alive	Alive : dead	Median day alive
None	0 : 8	1	0 : 8	5
NEW1 ¹	2 : 6	2	1 : 7	8
BVH-11B	1 : 7	3.5	8 : 0	>14
NEW12	6 : 2	>14	7 : 1	>14
BVH-3M	1 : 7	3	8 : 1	>14

EXAMPLE 13

5

This example illustrates the identification of additional BVH-3 and BVH-11 related sequences in Streptococcus species other than S. pneumoniae.

- 10 It was previously shown that BVH-3, BVH-11 and BVH-11-2 are a family of related proteins sharing common sequences. Homology searches were performed with the nucleotide sequence from the conserved region of these genes and compared with GenBank and EMBL sequences using FASTA. The
- 15 most significant homology was observed with a 2.469-kb gene coding for a calculated 92-kDa protein (**SEQ ID NO: 81**) of unknown function in S. agalactiae also called group B streptococcus or GBS. The gene was designated BVH-71. A protein demonstrating 99.2% identity and 99.5% similarity
- 20 with that of GBS was also identified in S. pyogenes also called group A streptococcus or GAS (**SEQ ID NO: 83**). The 5' region of the BVH-71 sequences (**SEQ ID NO: 80** and **SEQ ID NO: 82**), spanning nucleotides 1 to 717, demonstrated 58 and 60% identity with the conserved regions of BVH-3
- 25 (nucleotides 1 to 675) and BVH-11 (nucleotides 1 to 684) genes respectively. The first 239 amino acids of the translated sequences of the GBS and GAS BVH-71 open reading frames are 51 and 54% identical to the first 225 and 228 amino acids of BVH-3 and BVH-11, respectively. In addition
- 30 to structural similarities, streptococcal BVH-3, BVH-11 and BVH-71 proteins also share antigenic epitopes. A 97-kDa band was revealed on Western blots of GAS or GBS whole cells, using Mab H11-1.1-G11 reactive with the BVH-3 and BVH-11 conserved regions. Similarly, GAS and GBS

recombinant BVH-71 proteins were detected in Western immunoblot analysis.

- These results indicate that BVH-71, BVH-3 and BVH-11 proteins might share similar functions. Our results also
- 5 suggest that BVH-71 proteins can be used as protein vaccine components of anti-streptococcus. In a further embodiment BVH-71 proteins can be used as protein vaccine components of anti-GAS or anti-GBS vaccines.

What is claimed is:

1. An isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide having a sequence chosen from: SEQ ID NOs: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.
2. A polynucleotide according to claim 1, wherein said polynucleotide encodes a polypeptide having at least 95% identity to the second polypeptide.
3. An isolated polynucleotide encoding a polypeptide capable of generating antibodies having binding specificity for a polypeptide having a sequence chosen from: SEQ ID NOs: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.
4. An isolated polynucleotide that is complementary to the polynucleotide of claim 1.
5. An isolated polynucleotide that is complementary to the polynucleotide of claim 3.
6. The polynucleotide of claim 1, wherein said polynucleotide is DNA.
7. The polynucleotide of claim 3, wherein said polynucleotide is DNA.
8. The polynucleotide of claim 1, wherein said polynucleotide is RNA.
9. The polynucleotide of claim 3, wherein said polynucleotide is RNA.

10. A vector comprising the polynucleotide of claim 1, wherein said DNA is operably linked to an expression control region.
11. A vector comprising the polynucleotide of claim 3, wherein said DNA is operably linked to an expression control region.
12. A host cell transfected with the vector of claim 10.
13. A host cell transfected with the vector of claim 11.
14. A process for producing a polypeptide comprising culturing a host cell according to claim 12 under conditions suitable for expression of said polypeptide.
15. A process for producing a polypeptide comprising culturing a host cell according to claim 13 under condition suitable for expression of said polypeptide.
16. An isolated polypeptide having at least 70% identity to a second polypeptide having an amino acid sequence chosen from: SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.
17. An isolated polypeptide capable of generating antibodies having binding specificity for a second polypeptide having a sequence chosen from: SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.
18. An isolated polypeptide having an amino acid sequence chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

19. An isolated polypeptide according to claim 18, wherein the N-terminal Met residue is deleted.
20. An isolated polypeptide according to claim 18, wherein the secretory amino acid sequence is deleted.
21. A chimeric polypeptide comprising two or more polypeptides chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof; provided that the polypeptides or fragments, analogs or derivatives thereof are linked as to form a chimeric polypeptide.
22. A chimeric polypeptide comprising two or more polypeptides chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof; provided that the polypeptides or fragments, analogs or derivatives thereof are linked as to form a chimeric polypeptide.
23. A chimeric polypeptide of formula (I):
A-(B)_m-(C)_n-D (I)
Wherein;
m is 0 or 1,
n is 0 or 1,
A is chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof;
B is chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof;
C is chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof; and
D is chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55

to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

24. A chimeric polypeptide of formula (I):

$A-(B)_m-(C)_n-D$ (I)

Wherein;

m is 0 or 1,

n is 0 or 1,

A is chosen from SEQ ID NOs :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof;

B is chosen from SEQ ID NOs :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77, or fragments, analogs or derivatives thereof;

C is chosen from SEQ ID NOs :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof; and

D is chosen from SEQ ID NOs :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof.

25. A vaccine composition comprising a polypeptide according to any one of claims 16 to 24 and a pharmaceutically acceptable carrier, diluent or adjuvant.
26. A method for therapeutic or prophylactic treatment of meningitis, otitis media, bacteremia or pneumonia infection in an individual susceptible to meningitis, otitis media, bacteremia or pneumonia infection comprising administering to said individual a therapeutic or prophylactic amount of a composition according to claim 25.
27. A method for therapeutic or prophylactic treatment of streptococcal bacterial infection in an individual

susceptible to streptococcal infection comprising administering to said individual a therapeutic or prophylactic amount of a composition according to claim 25.

28. A method according to claim 26, wherein said individual is a mammal.
29. A method according to claim 27, wherein said individual is a human.
30. A method according to claim 22, wherein said bacterial infection is S.pneumoniae, group A streptococcus (*pyogenes*), group B streptococcus (GBS or *agalactiae*), *dysgalactiae*, *uberis*, *nocardia* or *Staphylococcus aureus*.
31. A method according to claim 26, wherein said bacterial infection is S.pneumoniae.
32. Use of a vaccine composition according to claim 25 for the prophylactic or therapeutic treatment of Streptococcal infection in an animal susceptible to or infected with streptococcal infection comprising administering to said animal a prophylactic or therapeutic amount of the composition.

ATGAAATTTA	GTAAAAAATA	TATAGCAGCT	GGATCAGCTG	TTATCGTATC	CTTGAGTCTA	60
TGTGCCTATG	CACTAAACCA	GCATCGTTTCG	CAGGAAAAATA	AGGACAATAA	TCGTGTCTCT	120
TATGTGGATG	GCAGCCAGTC	AAGTCAGAAA	AGTGAAAACT	TGACACCAGA	CCAGGTTAGC	180
CAGAAAGAAG	GAATTCAGGC	TGAGCAAATT	GTAATCAAAA	TTACAGATCA	GGGCTATGTA	240
ACGTCACACG	GTGACCACTA	TCATTACTAT	AATGGGAAAAG	TTCTTATGA	TGCCCTCTTT	300
AGTGAAGAAC	TCTTGATGAA	GGATCCAAAC	TATCAACTTA	AAGACGCTGA	TATTGTCAAT	360
GAAGTCAAGG	GTGGTTATAT	CATCAAGGTC	GATGGAAAAT	ATTATGTCTA	CCTGAAAGAT	420
GCAGCTCATG	CTGATAATGT	TCGAACTAAA	GATGAAATCA	ATCGTCAAAA	ACAAGAACAT	480
GTCAAAGATA	ATGAGAAGGT	TAACTCTAAT	GTTGCTGTAG	CAAGGTCTCA	GGGACGATAT	540
ACGACAAATG	ATGGTTATGT	CTTTAATCCA	GCTGATATTA	TCGAAGATAC	GGGTAATGCT	600
TATATCGTTC	CTCATGGAGG	TCACTATCAC	TACATTCCCA	AAAGCGATTT	ATCTGCTAGT	660
GAATTAGCAG	CAGCTAAAGC	ACATCTGGCT	GGAAAAAATA	TGCAACCGAG	TCAGTTAAGC	720
TATTCTTCAA	CAGCTAGTGA	CAATAACACG	CAATCTGTAG	CAAAAGGATC	AACTAGCAAG	780
CCAGCAAATA	AATCTGAAAA	TCTCCAGAGT	CTTTTGAAGG	AACTCTATGA	TTCACCTAGC	840
GCCCAACGTT	ACAGTGAATC	AGATGGCCTG	GTCTTTGACC	CTGCTAAGAT	TATCAGTCGT	900
ACACCAAATG	GAGTTGCGAT	TCCGCATGGC	GACCATTACC	ACTTTATTCC	TTACAGCAAG	960
CTTTCTGCTT	TAGAAGAAAA	GATTGCCAGA	ATGGTGCCTA	TCAGTGGAAC	TGGTTCTACA	1020
GTTTCTACAA	ATGCAAAACC	TAATGAAGTA	GTGTCTAGTC	TAGGCAGTCT	TTCAAGCAAT	1080
CCTTCTTCTT	TAACGACAAG	TAAGGAGCTC	TCTTCAGCAT	CTGATGGTTA	TATTTTAAAT	1140
CCAAAAGATA	TCGTTGAAGA	AACGGCTACA	GCCTTATATTG	TAAGACATGG	TGATCATTTT	1200
CATTACATTC	CAAAATCAAA	TCAAATGGGG	CAACCGACTC	TTCCAAACAA	TAGTCTAGCA	1260
ACACCTTCTC	CATCTCTTCC	AATCAATCCA	GGAACCTCAC	ATGAGAAACA	TGAAGAAGAT	1320
GGATACGGAT	TTGATGCTAA	TCGTATTATC	GCTGAAGATG	AATCAGGTTT	TGTCATGAGT	1380
CACGGAGACC	ACAATCATT	TTTCTTCAAG	AAGGACTTGA	CAGAAGAGCA	AATTAAGGCT	1440
GCGCAAAAAC	ATTTAGAGGA	AGTTAAAAC	AGTCATAATG	GATTAGATT	TTTGTCTAT	1500
CATGAACAGG	ATTATCCAGG	TAATGCCAAA	GAAATGAAAG	ATTTAGATAA	AAAAATCGAA	1560
GAAAAAATTG	CTGGCATTAT	GAAACAATAT	GGTGTCAAAC	GTGAAAGTAT	TGTCGTGAAT	1620
AAAGAAAAAA	ATGCGATTAT	TTATCCGCAT	GGAGATCACC	ATCATGCAGA	TCCGATTGAT	1680
GAACATAAAC	CGGTTGGAAT	TGGTCATTCT	CACAGTAACT	ATGAACGTG	TAAACCCGAA	1740
GAAGGAGTTG	CTAAAAAAGA	AGGGAATAAA	GTTTATACTG	GAGAAGAATT	AACGAATGTT	1800
GTTAATTGT	TAAAAAATAG	TACGTTTAAT	AATCAAAACT	TTACTCTAGC	CAATGGTCAA	1860
AAACGCGTTT	CTTTTAGTTT	TCCGCCTGAA	TTGGAGAAAA	AATTAGGTAT	CAATATGCTA	1920
GTAAATTTAA	TAACACCAGA	TGGAAAAGTA	TTGGAGAAAG	TATCTGGTAA	AGTATTTGGA	1980
GAAGGAGTAG	GGAATATTGC	AAACTTTGAA	TTAGATCAAC	CTTATTTACC	AGGACAAACA	2040
TTTAAGTATA	TATCGCTTC	AAAAGATTAT	CCAGAAGTAA	GTTATGATGG	TACATTTACA	2100
GTTCCAACCT	CTTTAGCTTA	CAAAATGGCC	AGTCAAAACGA	TTTTCTATCC	TTTCCATGCA	2160
GGGGATACTT	ATTTAAGAGT	GAACCCCTCA	TTTGCAGTGC	CTAAAGGAAC	TGATGCTTTA	2220
GTCAGAGTGT	TTGATGAATT	TCATGGAAAT	GCTTATTTAG	AAAATAACTA	TAAAGTTGGT	2280
GAAATCAAAT	TACCGATTCC	GAAATTAAAC	CAAGGAACAA	CCAGAACGGC	CGGAAATAAA	2340
ATTCTGTAA	CCTTCATGTC	AAATGCTTAT	TTGGACAATC	AATCGACTTA	TATTGTGGAA	2400
GTACCTATCT	TGGAAAAAGA	AAATCAAACT	GATAAACCAA	GTATTCTACC	ACAATTTAAA	2460
AGGAATAAAG	CACAAGAAAA	CTCAAACTT	GATGAAAAGG	TAGAAGAACC	AAAGACTAGT	2520
GAGAAGGTAG	AAAAAGAAAA	ACTTTCTGAA	ACTGGGAATA	GTAAGTAGTA	TTCAACGTTA	2580
GAAGAAGTTC	CTACAGTGGA	TCCTGTACAA	GAAAAAGTAG	CAAAATTTGC	TGAAAGTTAT	2640
GGGATGAAGC	TAGAAAATGT	CTTGTTTAAT	ATGGACGGAA	CAATTGAATT	ATATTTACCA	2700
TCAGGAGAAG	TCATTAAAAA	GAAATATGGCA	GATTTTACAG	GAGAAGCACC	TCAAGGAAAT	2760
GGTGAATAA	AACCATCTGA	AAATGGAAAA	GATTTTACAG	GAACAGTTGA	GAACCAACCA	2820
ACAGAAAAATA	AACCAGCAGA	TTCTTTACCA	GAGGCACCAA	ACGAAAAACC	TGTAACCA	2880
GAAAACTCAA	CGGATAATGG	AATGTTGAAT	CCAGAAGGGA	ATGTGGGGAG	TGACCCTATG	2940
TTAGATCCA	CATTAGAGGA	AGCTCCAGCA	GTAGATCCTG	TACAAGAAAA	ATTAGAAAAA	3000
TTTACAGCTA	GTTACGGATT	AGGCTTAGAT	AGTGTTATAT	TCAATATGGA	TGGAACGATT	3060
GAATTAAGAT	TGCCAAGTGG	AGAAGTGATA	AAAAAGAAAT	TATCTGATTT	CATAGCGTAA	3120

(SEQ ID NO: 1)

FIGURE 1

MKFSKKYIAA	GSAVIVLSL	CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	50
SENLTDPQVS	QKEGIAEQI	VIKITDQGYV	TSHGDHYHY	NGKVYPDALF	100
SEELLMKDPN	YQLKDADIVN	EVKGGYIIKV	DGKYVYVLKD	AAHADNVRTK	150
DEINRQKQEH	VKDNEKVNSN	VAVARSQGRY	TTNDGYVFNP	ADIIEDTGNA	200
YIVPHGGHYH	YIPKSDLAS	ELAAAKAHLA	GKNMQPSQLS	YSSTASDNNT	250
QSVAKGSTSK	PANKSENLOS	LLKELYDSPA	AQRYSESDGL	VFDPAKIISR	300
TPNGVAIPHG	DHYHFIPYSK	LSALEEKIAR	MVPISGTGST	VSTNAKPNEV	350
VSSLGSLSSN	PSSLTTSKEL	SSASDGYIFN	PKDIVEETAT	AYIVRHGDHF	400
HYIPKSNQIG	QPTLPNNSLA	TPSPSLPINP	GTSHEKHEED	GYGFDANRII	450
AEDESGFVMS	HGDHNHYFFK	KDLTEEQIKA	AQKHLEEVKT	SHNGLDLSLS	500
HEQDYPGNAK	EMKDLDKKIE	EKIAGIMKQY	GVKRESIVVN	KEKNAIYYPH	550
GDHHHADPID	EHKPVGIGHS	HSNYELFKPE	EGVAKKEGNK	VYTGEELTNV	600
VNLLKNSTFN	NQNFTLANGQ	KRVSFSPPE	LEKKLGINML	VKLITPDGKV	650
LEKVSQKVFQ	EGVGNIANFE	LDQPYLPGQT	FKYTIASKDY	PEVSYDGTFT	700
VPTSLAYKMA	SQTIFYPFHA	GDTYLRVNPQ	FAVPKGTDAL	VRVFDEPHGN	750
AYLENNYKVG	EIKLPIPKLN	QGTTRTAGNK	IPVTFMANAY	LDNQSTYIVE	800
VPILEKENQT	DKPSILPQFK	RNKAQENSKL	DEKVEEPKTS	EKVEKEKLSE	850
TGNSTSNSTL	EEVPTVDPVQ	EKVAKFAESY	GMKLENVLFN	MDGTIELYLP	900
SGEVIKKNMA	DFTGEAPQGN	GENKPSENGK	VSTGTVENQP	TENKPADSLP	950
EAPNEKPVKP	ENSTDNGMLN	PEGNVGSDPM	LDPALAEAPA	VDPVQEKLEK	1000
FTASYGLGLD	SVIFNMGTI	ELRLPSGEVI	KKNLSDFIA	(SEQ ID NO: 2)	1039

FIGURE 2

ATGAAATCA	ATAAAAAATA	TCTAGCTGGG	TCAGTAGCTA	CACTTGTTTT	AAGTGTCTGT	60
GCTTATGAAC	TAGGTTTGCA	TCAAGCTCAA	ACTGTAAAAG	AAAATAATCG	TGTTTCCTAT	120
ATAGATGGAA	AACAAGCGAC	GCAAAAAACG	GAGAATTTGA	CTCCTGATGA	GGTTAGCAAG	180
CGTGAAGGAA	TCAACGCCGA	ACAAATCGTC	ATCAAGATTA	CGGATCAAGG	TTATGTGACC	240
TCTCATGGAG	ACCATTATCA	TTACTATAAT	GGCAAGGTCC	CTTATGATGC	CATCATCAGT	300
GAAGAGCTCC	TCATGAAAGA	TCCGAATTAT	CAGTTGAAGG	ATTCAGACAT	TGTCAATGAA	360
ATCAAGGGTG	GTTATGTCAT	TAAGGTAAAC	GGTAAATACT	ATGTTTACCT	TAAGGATGCA	420
GCTCATGCGG	ATAATGTCCG	TACAAAAGAA	GAATCAATC	GGCAAAAACA	AGAACATAGT	480
CAGCATCGTG	AAGGAGGGAC	TTCAGCAAAC	GATGGTGCGG	TAGCCTTGC	ACGTTACACG	540
GGACGCTACA	CCACAGATGA	TGGTTATATC	TTCAATGCAT	CTGATATCAT	CGAAGATACG	600
GGCGATGCCT	ATATCGTTCC	TCATGGAGAT	CATTACCATT	ACATTCCTAA	GAATGAGTTA	660
TCAGCTAGCG	AGTTGGCTGC	TGCAGAAAGC	TTCTTATCTG	GTCGGGAAAA	TCTGTCAAAT	720
TTAAGAACCT	ATCGCCGACA	AAATAGCGAT	AACACTCCAA	GAACAACTG	GGTACCTTCT	780
GTAAGCAATC	CAGGAAGTAC	AAATACTAAC	ACAAGCAACA	ACAGCAACAC	TAACAGTCAA	840
GCAAGTCAAA	GTAATGACAT	TGATAGTCTC	TTGAAACAGC	TCTACAAACT	GCCTTTGAT	900
CAACGCCATG	TAGAATCTGA	TGGCCTTATT	TTCGACCCAG	CGCAAATCAC	AAGTCGAACC	960
GCCAGAGGTG	TAGCTGTCCC	TCATGGTAAC	CATTACCACT	TTATCCCTTA	TGAACAAATG	1020
TCTGAATTGG	AAAAACGAAT	TGCTCGTATT	ATTCCCTTTC	GTTATCGTTC	AAACCATTTG	1080
GTACCCAGATT	CAAGACCAGA	AGAACCAAGT	CCACAACCGA	CTCCAGAACC	TAGTCCAAGT	1140
CCGCAACCTG	CACCAAATCC	TCAACCAGCT	CCAAGCAATC	CAATTGATGA	GAAATTGGTC	1200
AAAGAAGCTG	TTCGAAAAGT	AGGCGATGGT	TATGTCTTTG	AGGAGAATGG	AGTTTCTCGT	1260
TATATCCCAG	CCAAGAATCT	TTCAGCAGAA	ACAGCAGCAG	GCATTGATAG	CAAACCTGGC	1320
AAGCAGGAAA	GTTTATCTCA	TAAGCTAGGA	GCTAAGAAAA	CTGACCTCCC	ATCTAGTGAT	1380
CGAGAATTTT	ACAATAAGGC	TTATGACTTA	CTAGCAAGAA	TTCACCAAGA	TTTACTTGAT	1440
AATAAAGGTC	GACAAGTTGA	TTTTGAGGCT	TGGATAACC	TGTTGGAACG	ACTCAAGGAT	1500
GTCTCAAGTG	ATAAAGTCAA	GTTAGTGAT	GATATTCTTG	CCTTCTTAGC	TCCGATTTCG	1560
CATCCAGAAC	GTTTAGGAAA	ACCAAATGCG	CAAATTACCT	ACACTGATGA	TGAGATTCAA	1620
GTAGCCAAGT	TGGCAGGCAA	GTACACAACA	GAAGACGGTT	ATATCTTTGA	TCCTCGTGAT	1680
ATAACCAAGT	ATGAGGGGGA	TGCCTATGTA	ACTCCACATA	TGACCCATAG	CCACTGGATT	1740
AAAAAAGATA	GTTTGTCTGA	AGCTGAGAGA	GCGGCAGCCC	AGGCTTATGC	TAAAGAGAAA	1800
GGTTTGACCC	CTCCTTCGAC	AGACCATCAG	GATTACAGGA	ATACTGAGGC	AAAAGGAGCA	1860
GAAGCTATCT	ACAACCGCGT	GAAAGCAGCT	AAGAAGGTGC	CACTTGATCG	TATGCCTTAC	1920
AATCTTCAAT	ATACTGTAGA	AGTCAAAAAC	GGTAGTTTAA	TCATACCTCA	TTATGACCAT	1980
TACCATAACA	TCAAATTTGA	GTGGTTTGAC	GAAGGCCTTT	ATGAGGCACC	TAAGGGGTAT	2040
ACTCTTGAGG	ATCTTTTGGC	GACTGTCAAG	TACTATGTCG	AACATCCAAA	CGAACGTCCG	2100
CATTTCAGATA	ATGGTTTGG	TAACGCTAGC	GACCATGTTT	AAAGAAACAA	AAATGGTCAA	2160
GCTGATACCA	ATCAAACGGA	AAAACCAAGC	GAGGAGAAAC	CTCAGACAGA	AAAACCTGAG	2220
GAAGAAACCC	CTCGAGAAGA	GAAACCACAA	AGCGAGAAAC	CAGAGTCTCC	AAAACCAACA	2280
GAGGAACCAG	AAGAAGAATC	ACCAGAGGAA	TCAGAAGAAC	CTCAGGTCGA	GACTGAAAAG	2340
GTTGAAGAAA	AACTGAGAGA	GGCTGAAGAT	TTACTTGGAA	AAATCCAGGA	TCCAATTATC	2400
AAGTCCAATG	CCAAAGAGAC	TCTCACAGGA	TTAAAAAATA	ATTTACTATT	TGGCACCCAG	2460
GACAACAATA	CTATTATGGC	AGAAGCTGAA	AAACTATTGG	CTTTATTAAA	GGAGAGTAAG	2520
TAA	(SEQ ID NO: 3)					2523

FIGURE 3

MKINKKYL	AG	SVATLVLSVC	AYELGLHQAQ	TVKENNRVSY	IDGKQATQKT	50
ENLTPDEV	SK	REGINAEQIV	IKITDQGYVT	SHGDHYHYYN	GKVPYDAIIS	100
EELLMKDP	NY	QLKDSDIVNE	IKGGYVIKVN	GKYYVYLKDA	AHADNVRTKE	150
EINRQKQEH	S	QHREGGTSAN	DGAVAFARSQ	GRYTDDGYI	FNASDIIEDT	200
GDAYIVPHGD		HYHYIPKNEL	SASELAAAEA	FLSGRENLSN	LRTYRRQNSD	250
NTPRTNWVPS		VSNPGTTNTN	TSNNSNTNSQ	ASQSNDDISL	LKQLYKLPLS	300
QRHVESDGLI		FDPAQITSRT	ARGVAVPHGN	HYHFIPYEQM	SELEKRIARI	350
IPLRYSRNNH		VPDSRPEEPS	PQPTPEPSPS	PQPAPNPQPA	PSNPIDEKLV	400
KEAVRKVGDG		YVFEENGVS	YIPAKNLSAE	TAAGIDSKLA	KQESLSHKL	450
AKKTDLPSSD		REFYNKAYDL	LARIHQDLLD	NKGRQVDFEA	LDNLLERLKD	500
VSSDKVKLVD		DILAFLAPIR	HPERLGKPN	QITYTDDEIQ	VAKLAGKYTT	550
EDGYIFDPRD		ITSDEGDAYV	TPHMTSHSWI	KKDSLSEAER	AAAQAYAKEK	600
GLTPPSTDHQ		DSGNTEAKGA	EAIYNRVKAA	KKVPLDRMPY	NLQYTVKVN	650
GSLIIPHYDH		YHNIKFEWFD	EGLYEAPKGY	TLEDLLATVK	YYVEHPNERP	700
HSDNFGNAS		DHVQRNKGQ	ADTNQTEKPS	EKPQTEKPE	EETPREKPKQ	750
SEKPESPKPT		EEPEEESPEE	SEEPQVETEK	VEEKLREAE	LLGKIQDPII	800
KSNAKETLTG		LKNLLFGTQ	DNNTIMAEAE	KLLALLKESK	(SEQ ID NO: 4)	840

FIGURE 4

ATGGAGAATA	TAGACATGTT	TAAATCAAAT	CATGAGCGAA	GAATGCGTTA	TTCCATTCGT	60
AAATTTAGTG	TAGGAGTAGC	TAGCGTAGCT	GTTGCCAGTC	TTTTATGGG	AAGTGTGTGA	120
CATGCGACAG	AGAAAGAGGG	AAGTACCCAA	GCAGCCACTT	CTTTAATAG	GGGAAATGGA	180
AGTCAGGCAG	AACAACGTGG	AGAACTCGAT	TTAGAACGAG	ATAAGGCAAT	GAAAGCGGTC	240
AGTGAATATG	TAGGAAAAAT	GGTGAGAGAT	GCCTATGTAA	AATCAGATAG	AAAACGACAT	300
AAAAATACTG	TAGCTCTAGT	TAACCACTTG	GGAAACATTA	AGAACAGGTA	TTTGAATGAA	360
ATAGTTCATT	CAACCTCAAA	AAGCCAACTA	CAGGAACTGA	TGATGAAGAG	TCAATCAGAA	420
GTAGATGAAG	CTGTGTCTAA	ATTTGAAAAG	GACTCATTTT	CTTCGTCAAG	TTCAGGATCC	480
TCCACTAAAC	CAGAAACTCC	GCAGCCGGAA	AATCCAGAGC	ATCAAAAACC	AACAACTCCA	540
TCTCCGGATA	CCAAACCAAG	CCCTCAACCA	GAAGGCAAGA	AACCAAGCGT	ACCAGACATT	600
AATCAGGAAA	AAGAAAAAGC	TAAGCTTGCT	GATGTAACCT	ACATGAGCAA	GATTTTAGAT	660
GATATACAAA	AACATCATCT	GCAGAAAGAA	AAACATCGTC	AGATTGTTGC	TCTTATTAAG	720
GAGCTTGATG	AGCTTAAAAA	GCAAGCTCTT	TCTGAAATTG	ATAATGTAAA	TACCAAGTA	780
GAAATTGAAA	ATACAGTCCA	CAAGATATTT	GCAGACATGG	ATGCAGTTGT	GACTAAATTC	840
AAAAAAGGCT	TAACTCAGGA	CACACCAAAA	GAACCAGGTA	ACAAAAAACC	ATCTGCTCCA	900
AAACCAGGTA	TGCAACCAAG	TCCTCAACCA	GAGGTTAAAC	CGCAGCTGGA	AAAACCAAAA	960
CCAGAGGTTA	AACCGCAACC	AGAAAAACCA	AAACCAGAGG	TTAAACCGCA	GCCGGAAAAA	1020
CCAAAACCA	AGGTTAAACC	GCAGCCGGAA	AAACCAAAAC	CAGAGGTTAA	ACCGCAGCCG	1080
GAAAAACCAA	AACCAGAGGT	TAAACCGCAG	CCGGAAAAAC	CAAAACCAGA	GGTTAAACCG	1140
CAGCCGGAAA	AACCAAAAACC	AGAGGTTAAA	CCGCAGCCGG	AAAAACCAAA	ACCAGAGGTT	1200
AAACCGCAGC	CGGAAAAACC	AAAACCAAG	GTTAAACCGC	AGCCGGAAAA	ACCAAAACCA	1260
GAGGTTAAAC	CGCAGCCGGA	AAAACCAAAA	CCAGAGGTTA	AACCGCAACC	AGAAAAACCA	1320
AAACCAGAGG	TTAAACCGCA	ACCAGAAAAA	CCAAAACCA	ATAATAGCAA	GCCACAAGCA	1380
GATGATAAGA	AGCCATCAAC	TACAAATAAT	TTAAGCAAGG	ACAAGCAACC	TTCTAACCAA	1440
GCTTCAACAA	ACGAAAAAGC	AACAAATAAA	CCGAAGAAGT	CATTGCCATC	AACTGGATCT	1500
ATTTCAAATC	TAGCACTTGA	AATTGCAGGT	CTTCTTACCT	TGGCGGGGGC	AACCATCTCT	1560
GCTAAGAA	GAATGAAATA	G	(SEQ ID NO: 5)			1581

FIGURE 5

MENIDMFKSN	HERRMYSIR	KFSVGVASVA	VASLFMGSVV	HATEKEGSTQ	50
AATSFNRNGG	SQAEQRGELD	LERDKAMKAV	SEYVGKMVRD	AYVKS DRKRH	100
KNTVALVNQL	GNIKNRYLNE	IVHSTSKSQL	QELMMKSQSE	VDEAVSKFEK	150
DSFSSSSSGS	STKPETPQPE	NPEHQKPTTP	SPDTKPSPQP	EGKKPSVPDI	200
NQEKEKAKLA	VVTYMSKILD	DIQKHHLQKE	KHRQIVALIK	ELDELKKQAL	250
SEIDNVNTKV	EIENTVHKIF	ADMDAVVTKF	KKGLTQDTPK	EPGNKKPSAP	300
KPGMQPSPQP	EVKPQLEKPK	PEVKPQPEKP	KPEVKPQPEK	PKPEVKPQPE	350
KPKPEVKPQP	EKPKPEVKPQ	PEKPKPEVKP	QPEKPKPEVK	PQPEKPKPEV	400
KPQPEKPKPE	VKPQPEKPKP	EVKPQPEKPK	PEVKPQPEKP	KPEVKPQPEK	450
PKPDNSKPQA	DDKKPSTTNN	LSKDKQPSNQ	ASTNEKATNK	PKKSLPSTGS	500
ISNLALEIAG	LLTLGATIL	AKKRMK	(SEQ ID NO: 6)	526	

FIGURE 6

ATGAAATTTA	GTA AAAAATA	TATAGCAGCT	GGATCAGCTG	TTATCGTATC	CTTGAGTCTA	60
TGTGCCTATG	CACTAAACCA	GCATCGTTCTG	CAGGAAAAATA	AGGACAATAA	TCGTGTCTCT	120
TATGTGGATG	GCAGCCAGTC	AAGTCAGAAA	AGTGAAAACT	TGACACCAGA	CCAGGTTAGC	180
CAGAAAGAAG	GAATTCAGGC	TGAGCAAATT	GTAATCAAAA	TTACAGATCA	GGGCTATGTA	240
ACGTACACACG	GTGACCACTA	TCATTACTAT	AATGGGAAAG	TTCTTATGA	TGCCCTCTTT	300
AGTGAAGAAC	TCTTGATGAA	GGATCCAAAC	TATCAACTTA	AAGACGCTGA	TATTGTCAAT	360
GAAGTCAAGG	GTGGTTATAT	CATCAAGGTC	GATGAAAAAT	ATTATGTCTA	CCTGAAAGAT	420
GCAGCTCATG	CTGATAATGT	TCGAACTAAA	GATGAAATCA	ATCGTCAAAA	ACAAGAACAT	480
GTCAAAGATA	ATGAGAAGGT	TAACTCTAAT	GTGCTGTAG	CAAGGTCTCA	GGGACGATAT	540
ACGACAAATG	ATGGTTATGT	CTTTAATCCA	GCTGATATTA	TCGAAGATAC	GGGTAATGCT	600
TATATCGTTC	CTCATGGAGG	TCATATCAC	TACATTCCCA	AAAGCGATTT	ATCTGCTAGT	660
GAATTAGCAG	CAGCTAAAGC	ACATCTGGCT	GGAAAAATA	TGCAACCGAG	TCAGTTAAGC	720
TATTCTTCAA	CAGCTAGTGA	CAATAACACG	CAATCTGTAG	CAAAAGGATC	AACTAGCAAG	780
CCAGCAAATA	AATCTGAAAA	TCTCCAGAGT	CTTTTGAAGG	AACTCTATGA	TTCACCTAGC	840
GCCCAACGTT	ACAGTGAATC	AGATGGCCTG	GTCTTTGACC	CTGCTAAGAT	TATCAGTCGT	900
ACACCAAATG	GAGTTGCGAT	TCCGCATGGC	GACCATTACC	ACTTTATTCC	TTACAGCAAG	960
CTTTCTGCTT	TAGAAGAAAA	GATTGCCAGA	ATGGTGCCTA	TCAGTGGAAC	TGGTTCTACA	1020
GTTTCTACAA	ATGCAAAACC	TAATGAAGTA	GTGTCTAGTC	TAGGCAGTCT	TTCAAGCAAT	1080
CCTTCTTCTT	TAACGACAAG	TAAGGAGCTC	TCTTCAGCAT	CTGATGGTTA	TATTTTAAAT	1140
CCAAAAGATA	TCGTTGAAGA	AACGGCTACA	GCTTATATTG	TAAGACATGG	TGATCATTTC	1200
CATTACATTC	CAAAATCAAA	TCAAATTGGG	CAACCGACTC	TTCCAAACAA	TAGTCTAGCA	1260
ACACCTTCTC	CATCTCTTCC	AATCAATCCA	GGAACCTCAC	ATGAGAAACA	TGAAGAAGAT	1320
GGATACGGAT	TTGATGCTAA	TCGTATTATC	GCTGAAGATG	AATCAGGTTT	TGTCATGAGT	1380
CACGGAGACC	ACAATCATTA	TTTCTTCAAG	AAGGACTTGA	CAGAAGAGCA	AATTAAGGTG	1440
CGCAAAACA	TTTAG	(SEQ ID NO: 7)				1455

FIGURE 7

MKFSKKYIAA	GSAVIVLSLSL	CAYALNQHRS	QENKDNNRVS	YVDGSQSSQK	50
SENLTDPQVS	QKEGIAEQI	VIKITDQGYV	TSHGDHYHY	NGKVPYDALF	100
SEELLMKDPN	YQLKDADIVN	EVKGGYIIKV	DGKYVYVYLD	AAHADNVRTK	150
DEINRQKQEH	VKONEKVNSN	VAVARSQGRY	TTNDGYVFPN	ADIIEDTGNA	200
YIVPHGGHYH	YIPKSDLSAS	ELAAAKAHLA	GKNMQPSQLS	YSSTASDNNT	250
QSVAKGSTSK	PANKSENLOS	LLKELYDSPA	AQRYSESDGL	VFDPAKIISR	300
TPNGVAIPHG	DHYHFIPYSK	LSALEEKIAR	MVPISGTGST	VSTNAKPNEV	350
VSSLGSLSSN	PSSLTTSKEL	SSASDGYIFN	PKDIVEETAT	AYIVRHGDHF	400
HYIPKSNQIG	QPTLPNNLSA	TPSPSLPINP	GTSHEKHEED	GYGFDANRII	450
AEDESGFVMS	HGDHNNHYFFK	KDLTEEQIKV	RKNI	(SEQ ID NO: 8)	484

FIGURE 8

ATGAAAGATT	TAGATAAAAA	AATCGAAGAA	AAAATTGCTG	GCATTATGAA	ACAATATGGT	60
GTCAAACGTG	AAAGTATTGT	CGTGAATAAA	GAAAAAATG	CGATTATTTA	TCCGCATGGA	120
GATCACCATC	ATGCAGATCC	GATTGATGAA	CATAAACCGG	TTGGAATTGG	TCATTCTCAC	180
AGTAACTATG	AACTGTTTAA	ACCCGAAGAA	GGAGTTGCTA	AAAAAGAAGG	GAATAAAGTT	240
TATACTGGAG	AAGAATTAAC	GAATGTTGTT	AATTTGTTAA	AAAATAGTAC	GTTTAATAAT	300
CAAAACTTTA	CTCTAGCCAA	TGGTCAAAAA	CGCGTTTCTT	TTAGTTTTCC	GCCTGAATTG	360
GAGAAAAAAT	TAGGTATCAA	TATGCTAGTA	AAATTAATAA	CACCAGATGG	AAAAGTATTG	420
GAGAAAAGTAT	CTGGTAAAGT	ATTTGGAGAA	GGAGTAGGGA	ATATTGCAAA	CTTTGAATTA	480
GATCAACCTT	ATTTACCAGG	ACAAACATTT	AAGTATACTA	TCGCTTCAAA	AGATTATCCA	540
GAAGTAAGTT	ATGATGGTAC	ATTTACAGTT	CCAACCTCTT	TAGCTTACAA	AATGGCCAGT	600
CAAACGATTT	TCTATCCTTT	CCATGCAGGG	GATACTTATT	TAAGAGTGAA	CCCTCAATTT	660
GCAGTGCCTA	AAGGAACTGA	TGCTTTAGTC	AGAGTGTTTG	ATGAATTTC	TGGAAATGCT	720
TATTTAGAAA	ATAACTATAA	AGTTGGTGAA	ATCAAATTAC	CGATTCCGAA	ATTAAACCAA	780
GGAACAACCA	GAACGGCCGG	AAATAAAATT	CCTGTAACCT	TCATGGCAAA	TGCTTATTTG	840
GACAATCAAT	CGACTTATAT	TGTGGAAGTA	CCTATCTTGG	AAAAAGAAAA	TCAAACGTAT	900
AAACCAAGTA	TTCTACCACA	ATTTAAAAGG	AATAAAGCAC	AAGAAAACTC	AAAACCTGAT	960
GAAAAGGTAG	AAGAACCAAA	GACTAGTGAG	AAGGTAGAAA	AAGAAAAACT	TTCTGAAACT	1020
GGGAATAGTA	CTAGTAATTC	AACGTTAGAA	GAAGTTCCTA	CAGTGGATCC	TGTACAAGAA	1080
AAAGTAGCAA	AATTTGCTGA	AAGTTATGGG	ATGAAGCTAG	AAAATGTCTT	GTTTAATATG	1140
GACGGAACAA	TTGAATTATA	TTTACCATCA	GGAGAAGTCA	TTAAAAAGAA	TATGGCAGAT	1200
TTTACAGGAG	AAGCACCTCA	AGGAAATGGT	GAAAAATAAC	CATCTGAAAA	TGGAAAAGTA	1260
TCTACTGGAA	CAGTTGAGAA	CCAACCAACA	GAAAAATAAC	CAGCAGATTC	TTTACCAGAG	1320
GCACCAAACG	AAAAACCTGT	AAAACCAGAA	AACTCAACGG	ATAATGGAAT	GTTGAATCCA	1380
GAAGGGGAATG	TGGGGAGTGA	CCCTATGTTA	GATCCAGCAT	TAGAGGAAGC	TCCAGCAGTA	1440
GATCCTGTAC	AAGAAAAATT	AGAAAAATTT	ACAGCTAGTT	ACGGATTAGG	CTTAGATAGT	1500
GTTATATTCA	ATATGGATGG	AACGATTGAA	TTAAGATTGC	CAAGTGGAGA	AGTGATAAAA	1560
AAGAATTTAT	CTGATTTTCAT	AGCGTAA	(SEQ ID NO: 9)			1587

FIGURE 9

MKDLDKKIEE	KIAGIMKQYG	VKRESIVVNK	EKNAIYYPHG	DHHHADPIDE	50
HKPVGIGHSH	SNYELFKPEE	GVAKKEGNKV	YTGEELTNVV	NLLKNSTFNN	100
QNFTLANGQK	RVSFSFPPEL	EKKLGINMLV	KLITPDGKVL	EKVSGKVFG	150
GVGNIANFEL	DQPYLPGQTF	KYTIASKDYP	EVSYDGTFTV	PTSLAYKMAS	200
QTIFYPPFHAG	DTYLRVNPQF	AVPKGTDALV	RVFDEFHGNA	YLENNYKVGE	250
IKLPIPKLNQ	GTTRTAGNKI	PVTFMANAYL	DNQSTYIVEV	PILEKENQTD	300
KPSILPQFKR	NKAQENSKLD	EKVEEPTSE	KVEKEKLSET	GNSTSNSTLE	350
EVPTVDPVQE	KVAKFAESYG	MKLENVLFNM	DGTIELYLPS	GEVIKKNMAD	400
FTGEAPQGNG	ENKPSENGKV	STGTVENQPT	ENKPADSLPE	APNEKPVKPE	450
NSTDNGMLNP	EGNVGSDPML	DPALEEAPAV	DPVQEKLEKF	TASYGLGLDS	500
VIFNMDGTIE	LRLPSGEVIK	KNLSDFIA	(SEQ ID NO: 10)		528

FIGURE 10

BVH3	WU2	1	CAYALNQHRSQENKDNRRVSYVDGSQSSQKSENLT	PDQVSQKEGIAEQIVIKITDQGYV	60	
BVH3	RX1	1	CAYALNQHRSQENKDNRRVSYVDGSQSSQKSENLT	PDQVSQKEGIAEQIVIKITDQGYV	60	
BVH3	JNR7/87	1	CAYALNQHRSQENKDNRRVSYVDGSQSSQKSENLT	PDQVSQKEGIAEQIVIKITDQGYV	60	
BVH3	SP64	1	CAYALNQHRSQENKDNRRVSYVDGSQSSQKSENLT	PDQVSQKEGIAEQIVIKITDQGYV	60	
BVH3	P4241	1	CAYALNQHRSQENKDNRRVSYVDGSQSSQKSENLT	PDQVSQKEGIAEQIVIKITDQGYV	60	
BVH3	A66	1	CAYALNQHRSQENKDNRRVSYVDGSQSSQKSENLT	PDQVSQKEGIAEQIVIKITDQGYV	60	

BVH3	WU2	61	TSHGDHYHYNGKVPYDALFSEELLMKDPNYQLK	DADIVNEVKGGYIIKVDGKYVYVLKD	120	
BVH3	RX1	61	TSHGDHYHYNGKVPYDALFSEELLMKDPNYQLK	DADIVNEVKGGYIIKVDGKYVYVLKD	120	
BVH3	JNR7/87	61	TSHGDHYHYNGKVPYDALFSEELLMKDPNYQLK	DADIVNEVKGGYIIKVDGKYVYVLKD	120	
BVH3	SP64	61	TSHGDHYHYNGKVPYDALFSEELLMKDPNYQLK	DADIVNEVKGGYIIKVDGKYVYVLKD	120	
BVH3	P4241	61	TSHGDHYHYNGKVPYDALFSEELLMKDPNYQLK	DADIVNEVKGGYIIKVDGKYVYVLKD	120	
BVH3	A66	61	TSHGDHYHYNGKVPYDALFSEELLMKDPNYQLK	DADIVNEVKGGYIIKVDGKYVYVLKD	120	

BVH3	WU2	121	AAHADNVRTKDEINRQKQEHVKDNEKVN	SNVAVARSQGRYTTNDGYVFNPAIDIEDTGNA	180	
BVH3	RX1	121	AAHADNVRTKDEINRQKQEHVKDNEKVN	SNVAVARSQGRYTTNDGYVFNPAIDIEDTGNA	180	
BVH3	JNR7/87	121	AAHADNVRTKDEINRQKQEHVKDNEKVN	SNVAVARSQGRYTTNDGYVFNPAIDIEDTGNA	180	
BVH3	SP64	121	AAHADNVRTKDEINRQKQEHVKDNEKVN	SNVAVARSQGRYTTNDGYVFNPAIDIEDTGNA	180	
BVH3	P4241	121	AAHADNVRTKDEINRQKQEHVKDNEKVN	SNVAVARSQGRYTTNDGYVFNPAIDIEDTGNA	180	
BVH3	A66	121	AAHADNVRTKDEINRQKQEHVKDNEKVN	SNVAVARSQGRYTTNDGYVFNPAIDIEDTGNA	180	

BVH3	WU2	181	YIVPHRGHYHYIPKSDLSASELAAAKAHLAGKN	MQPSQLSYSSTASDNNTQSVAKGSTSK	240	
BVH3	RX1	181	YIVPHRGHYHYIPKSDLSASELAAAKAHLAGKN	MQPSQLSYSSTASDNNTQSVAKGSTSK	240	
BVH3	JNR7/87	181	YIVPHRGHYHYIPKSDLSASELAAAKAHLAGKN	MQPSQLSYSSTASDNNTQSVAKGSTSK	240	
BVH3	SP64	181	YIVPHRGHYHYIPKSDLSASELAAAKAHLAGKN	MQPSQLSYSSTASDNNTQSVAKGSTSK	240	
BVH3	P4241	181	YIVPHRGHYHYIPKSDLSASELAAAKAHLAGKN	MQPSQLSYSSTASDNNTQSVAKGSTSK	240	
BVH3	A66	181	YIVPHRGHYHYIPKSDLSASELAAAKAHLAGKN	MQPSQLSYSSTASDNNTQSVAKGSTSK	240	

BVH3	WU2	241	PANKSENLSLLKELYDSPAQRYS	ESDGLVFDPAKIIISRTPNGVAIPHGDHYHFIPYSK	300	
BVH3	RX1	241	PANKSENLSLLKELYDSPAQRYS	ESDGLVFDPAKIIISRTPNGVAIPHGDHYHFIPYSK	300	
BVH3	JNR7/87	241	PANKSENLSLLKELYDSPAQRYS	ESDGLVFDPAKIIISRTPNGVAIPHGDHYHFIPYSK	300	
BVH3	SP64	241	PANKSENLSLLKELYDSPAQRYS	ESDGLVFDPAKIIISRTPNGVAIPHGDHYHFIPYSK	300	
BVH3	P4241	241	PANKSENLSLLKELYDSPAQRYS	ESDGLVFDPAKIIISRTPNGVAIPHGDHYHFIPYSK	300	
BVH3	A66	241	PANKSENLSLLKELYDSPAQRYS	ESDGLVFDPAKIIISRTPNGVAIPHGDHYHFIPYSK	300	

BVH3	WU2	301	LSALEEKIARMVPISGTGSTVSTNAKPNEVVSSL	GLSSNPSSLTTSKELSSASDGYIFN	360	
BVH3	RX1	301	LSALEEKIARMVPISGTGSTVSTNAKPNEVVSSL	GLSSNPSSLTTSKELSSASDGYIFN	360	
BVH3	JNR7/87	301	LSALEEKIARMVPISGTGSTVSTNAKPNEVVSSL	GLSSNPSSLTTSKELSSASDGYIFN	360	
BVH3	SP64	301	LSALEEKIARMVPISGTGSTVSTNAKPNEVVSSL	GLSSNPSSLTTSKELSSASDGYIFN	360	
BVH3	P4241	301	LSALEEKIARMVPISGTGSTVSTNAKPNEVVSSL	GLSSNPSSLTTSKELSSASDGYIFN	360	
BVH3	A66	301	LSALEEKIARMVPISGTGSTVSTNAKPNEVVSSL	GLSSNPSSLTTSKELSSASDGYIFN	360	

BVH3	WU2	361	PKDIVEETATAYIVRHGDHFHYIPKSNQIGQPTLP	NNSLATPSPSLPINPGTSHEKHEED	420	
BVH3	RX1	361	PKDIVEETATAYIVRHGDHFHYIPKSNQIGQPTLP	NNSLATPSPSLPINPGTSHEKHEED	420	
BVH3	JNR7/87	361	PKDIVEETATAYIVRHGDHFHYIPKSNQIGQPTLP	NNSLATPSPSLPINPGTSHEKHEED	420	
BVH3	SP64	361	PKDIVEETATAYIVRHGDHFHYIPKSNQIGQPTLP	NNSLATPSPSLPINPGTSHEKHEED	420	
BVH3	P4241	361	PKDIVEETATAYIVRHGDHFHYIPKSNQIGQPTLP	NNSLATPSPSLPINPGTSHEKHEED	420	
BVH3	A66	361	PKDIVEETATAYIVRHGDHFHYIPKSNQIGQPTLP	NNSLATPSPSLPINPGTSHEKHEED	420	

BVH3	WU2	421	GYGFDANRIIAEDES	GFVMSHGDHNYFFKDLTEEQIKAAQKHLEEVKTS	SHNGLDSLSS	480
BVH3	RX1	421	GYGFDANRIIAEDES	GFVMSHGDHNYFFKDLTEEQIKAAQKHLEEVKTS	SHNGLDSLSS	480
BVH3	JNR7/87	421	GYGFDANRIIAEDES	GFVMSHGDHNYFFKDLTEEQIKAAQKHLEEVKTS	SHNGLDSLSS	480
BVH3	SP64	421	GYGFDANRIIAEDES	GFVMSHGDHNYFFKDLTEEQIKAAQKHLEEVKTS	SHNGLDSLSS	480
BVH3	P4241	421	GYGFDANRIIAEDES	GFVMSHGDHNYFFKDLTEEQIKAAQKHLEEVKTS	SHNGLDSLSS	480
BVH3	A66	421	GYGFDANRIIAEDES	GFVMSHGDHNYFFKDLTEEQIKAAQKHLEEVKTS	SHNGLDSLSS	480

BVH3 WU2	481	HEQDYPSNAKEMKDLKKIEEKIAGIMKQYGVKRESIVVNKEKNAIYPHGDHHDADPID	540
BVH3 RX1	481	HEQDYPSNAKEMKDLKKIEEKIAGIMKQYGVKRESIVVNKEKNAIYPHGDHHDADPID	540
BVH3 JNR7/87	481	HEQDYPSNAKEMKDLKKIEEKIAGIMKQYGVKRESIVVNKEKNAIYPHGDHHDADPID	540
BVH3 SP64	481	HEQDYPSNAKEMKDLKKIEEKIAGIMKQYGVKRESIVVNKEKNAIYPHGDHHDADPID	540
BVH3 P4241	481	HEQDYPSNAKEMKDLKKIEEKIAGIMKQYGVKRESIVVNKEKNAIYPHGDHHDADPID	540
BVH3 A66	481	HEQDYPSNAKEMKDLKKIEEKIAGIMKQYGVKRESIVVNKEKNAIYPHGDHHDADPID	540
.....			
BVH3 WU2	541	EHKPVGIGHSHSNYELFKPEEGVAKKEGNKVYTGEELTNVNNLLKNSTFNNQNFTLANGQ	600
BVH3 RX1	541	EHKPVGIGHSHSNYELFKPEEGVAKKEGNKVYTGEELTNVNNLLKNSTFNNQNFTLANGQ	600
BVH3 JNR7/87	541	EHKPVGIGHSHSNYELFKPEEGVAKKEGNKVYTGEELTNVNNLLKNSTFNNQNFTLANGQ	600
BVH3 SP64	541	EHKPVGIGHSHSNYELFKPEEGVAKKEGNKVYTGEELTNVNNLLKNSTFNNQNFTLANGQ	600
BVH3 P4241	541	EHKPVGIGHSHSNYELFKPEEGVAKKEGNKVYTGEELTNVNNLLKNSTFNNQNFTLANGQ	600
BVH3 A66	541	EHKPVGIGHSHSNYELFKPEEGVAKKEGNKVYTGEELTNVNNLLKNSTFNNQNFTLANGQ	600
.....			
BVH3 WU2	601	KRVSFSPFPELEKKGINMLVKLITPDGKVKLEKVSQKVFEGGVGNIANFELDQPYLPQQT	660
BVH3 RX1	601	KRVSFSPFPELEKKGINMLVKLITPDGKVKLEKVSQKVFEGGVGNIANFELDQPYLPQQT	660
BVH3 JNR7/87	601	KRVSFSPFPELEKKGINMLVKLITPDGKVKLEKVSQKVFEGGVGNIANFELDQPYLPQQT	660
BVH3 SP64	601	KRVSFSPFPELEKKGINMLVKLITPDGKVKLEKVSQKVFEGGVGNIANFELDQPYLPQQT	660
BVH3 P4241	601	KRVSFSPFPELEKKGINMLVKLITPDGKVKLEKVSQKVFEGGVGNIANFELDQPYLPQQT	660
BVH3 A66	601	KRVSFSPFPELEKKGINMLVKLITPDGKVKLEKVSQKVFEGGVGNIANFELDQPYLPQQT	660
.....			
BVH3 WU2	661	FKYTIASKDYPEVSYDGTFTVPTSLAYKMASQTIFFYPFHAGDTYLRVNPQFAVPKGTDAL	720
BVH3 RX1	661	FKYTIASKDYPEVSYDGTFTVPTSLAYKMASQTIFFYPFHAGDTYLRVNPQFAVPKGTDAL	720
BVH3 JNR7/87	661	FKYTIASKDYPEVSYDGTFTVPTSLAYKMASQTIFFYPFHAGDTYLRVNPQFAVPKGTDAL	720
BVH3 SP64	661	FKYTIASKDYPEVSYDGTFTVPTSLAYKMASQTIFFYPFHAGDTYLRVNPQFAVPKGTDAL	720
BVH3 P4241	661	FKYTIASKDYPEVSYDGTFTVPTSLAYKMASQTIFFYPFHAGDTYLRVNPQFAVPKGTDAL	720
BVH3 A66	661	FKYTIASKDYPEVSYDGTFTVPTSLAYKMASQTIFFYPFHAGDTYLRVNPQFAVPKGTDAL	720
.....			
BVH3 WU2	721	VRVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE	780
BVH3 RX1	721	VRVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE	780
BVH3 JNR7/87	721	VRVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE	780
BVH3 SP64	721	VRVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE	780
BVH3 P4241	721	VRVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE	780
BVH3 A66	721	VRVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE	780
.....			
BVH3 WU2	781	VPILEKENQTDKPSILPQFKRNKAQENSKFDEKVEEPTSEKVEKEKLSGTGNSTSNSTL	840
BVH3 RX1	781	VPILEKENQTDKPSILPQFKRNKAQENSKLDEKVEEPTSEKVEKEKLSGTGNSTSNSTL	840
BVH3 JNR7/87	781	VPILEKENQTDKPSILPQFKRNKAQENSKLDEKVEEPTSEKVEKEKLSGTGNSTSNSTL	840
BVH3 SP64	781	VPILEKENQTDKPSILPQFKRNKAQENSKLDEKVEEPTSEKVEKEKLSGTGNSTSNSTL	840
BVH3 P4241	781	VPILEKENQTDKPSILPQFKRNKAQENSKFDEKVEEPTSEKVEKEKLSGTGNSTSNSTL	840
BVH3 A66	781	VPILEKENQTDKPSILPQFKRNKAQENSKFDEKVEEPTSEKVEKEKLSGTGNSTSNSTL	840
.....			
BVH3 WU2	841	EEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPSSGEVIKQNMADFTGEAPQGN	900
BVH3 RX1	841	EEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPSSGEVIKQNMADFTGEAPQGN	900
BVH3 JNR7/87	841	EEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPSSGEVIKQNMADFTGEAPQGN	900
BVH3 SP64	841	EEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPSSGEVIKQNMADFTGEAPQGN	900
BVH3 P4241	841	EEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPSSGEVIKQNMADFTGEAPQGN	900
BVH3 A66	841	EEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPSSGEVIKQNMADFTGEAPQGN	900
.....			
BVH3 WU2	901	GENKPSSENGKVSTGTVENQPTENKPADSLPEAPNEKPVKPENSTONGMLNPEGNVGSDPM	960
BVH3 RX1	901	GENKPSSENGKVSTGTGTVENQPTENKPADSLPEAPNEKPVKPENSTONGMLNPEGNVGSDPM	960
BVH3 JNR7/87	901	GENKPSSENGKVSTGTGTVENQPTENKPADSLPEAPNEKPVKPENSTONGMLNPEGNVGSDPM	960
BVH3 SP64	901	GENKPSSENGKVSTGTGTVENQPTENKPADSLPEAPNEKPVKPENSTONGMLNPEGNVGSDPM	960
BVH3 P4241	901	GENKPSSENGKVSTGTGTVENQPTENKPADSLPEAPNEKPVKPENSTONGMLNPEGNVGSDPM	960
BVH3 A66	901	GENKPSSENGKVSTGTGTVENQPTENKPADSLPEAPNEKPVKPENSTONGMLNPEGNVGSDPM	960
.....			
BVH3 WU2	961	LDPALEEAAPVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKKNLSDLIA	1019
BVH3 RX1	961	LDPALEEAAPVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKKNLSDLIA	1019
BVH3 JNR7/87	961	LDPALEEAAPVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKKNLSDLIA	1019
BVH3 SP64	961	LDPALEEAAPVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKKNLSDLIA	1019
BVH3 P4241	961	LDPALEEAAPVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKKNLSDLIA	1019
BVH3 A66	961	LDPALEEAAPVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKKNLSDLIA	1019
.....			

FIGURE 11

BVH11-2 SP64 1 CSYELGRHQAGQVKKESNRVSYIDGDQAGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11-2 JNR7/87 1 CSYELGRHQAGQVKKESNRVSYIDGDQAGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11-2 P4241 1 CSYELGRHQAGQDKKESNRVAYIDGDQAGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11-2 A66 1 CSYELGRHQAGQDKKESNRVAYIDGDQAGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11-2 WU2 1 CSYELGRHQAGQDKKESNRVAYIDGDQAGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11-2 Rx1 1 CSYELGRHQAGQVKKESNRVSYIDGDQAGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 P4241 1 CSYELGRHQAGQDKKESNRVAYIDGDQAGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 WU2 1 CSYELGRHQAGQDKKESNRVAYIDGDQAGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 A66 1 CSYELGRHQAGQDKKESNRVAYIDGDQAGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 Rx1 1 CSYELGRHQAGQVKKESNRVSYIDGDQAGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 JNR7/87 1 CSYELGRHQAGQDKKESNRVAYIDGDQAGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 SP63 1 CSYELGRHQAGQVKKESNRVSYIDGDQAGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 SP64 1 CAYELGLHQA-QTVKENNRVSYIDGKQATQKTENLTPDEVSKREGINAEQIVIKITDQGY 59

BVH11-2 SP64 61 VTSBGDHYHYNGKVPYDAI ISEELMKDPNYQLKSDIVNEIKGGYVIKVDGKYVYVLK 120
BVH11-2 JNR7/87 61 VTSBGDHYHYNGKVPYDAI ISEELMKDPNYQLKSDIVNEIKGGYVIKVDGKYVYVLK 120
BVH11-2 P4241 61 VTSBGDHYHYNGKVPYDAI ISEELMKDPNYQLKSDIVNEIKGGYVIKVDGKYVYVLK 120
BVH11-2 A66 61 VTSBGDHYHYNGKVPYDAI ISEELMKDPNYQLKSDIVNEIKGGYVIKVDGKYVYVLK 120
BVH11-2 WU2 61 VTSBGDHYHYNGKVPYDAI ISEELMKDPNYQLKSDIVNEIKGGYVIKVDGKYVYVLK 120
BVH11-2 Rx1 61 VTSBGDHYHYNGKVPYDAI ISEELMKDPNYQLKSDIVNEIKGGYVIKVDGKYVYVLK 120
BVH11 P4241 61 VTSBGDHYHYNGKVPYDAI ISEELMKDPNYQLKSDIVNEIKGGYVIKVDGKYVYVLK 120
BVH11 WU2 61 VTSBGDHYHYNGKVPYDAI ISEELMKDPNYQLKSDIVNEIKGGYVIKVDGKYVYVLK 120
BVH11 A66 61 VTSBGDHYHYNGKVPYDAI ISEELMKDPNYQLKSDIVNEIKGGYVIKVDGKYVYVLK 120
BVH11 Rx1 61 VTSBGDHYHYNGKVPYDAI ISEELMKDPNYQLKSDIVNEIKGGYVIKVDGKYVYVLK 120
BVH11 JNR7/87 61 VTSBGDHYHYNGKVPYDAI ISEELMKDPNYQLKSDIVNEIKGGYVIKVDGKYVYVLK 120
BVH11 SP63 61 VTSBGDHYHYNGKVPYDAI ISEELMKDPNYQLKSDIVNEIKGGYVIKVDGKYVYVLK 120
BVH11 SP64 60 VTSBGDHYHYNGKVPYDAI ISEELMKDPNYQLKSDIVNEIKGGYVIKVDGKYVYVLK 119

BVH11-2 SP64 121 DAAHADNIRTKEEIKRQKQEHSHNHSRA---DNAAAAAAGQRYTTDDGYIFNASDIIE 177
BVH11-2 JNR7/87 121 DAAHADNIRTKEEIKRQKQEHSHNHGGGSN--DQAVVAARAQGRYTTDDGYIFNASDIIE 178
BVH11-2 P4241 121 DAAHADNIRTKEEIKRQKQEHSHNHGGGSN--DQAVVAARAQGRYTTDDGYIFNASDIIE 178
BVH11-2 A66 121 DAAHADNIRTKEEIKRQKQEHSHNHGGGSN--DQAVVAARAQGRYTTDDGYIFNASDIIE 178
BVH11-2 WU2 121 DAAHADNIRTKEEIKRQKQEHSHNHGGGSN--DQAVVAARAQGRYTTDDGYIFNASDIIE 178
BVH11-2 Rx1 121 DAAHADNIRTKEEIKRQKQEHSHNHSRA---DNAAAAAAGQRYTTDDGYIFNASDIIE 177
BVH11 P4241 121 DAAHADNIRTKEEIKRQKQEHSHNHGGGSN--DQAVVAARAQGRYTTDDGYIFNASDIIE 178
BVH11 WU2 121 DAAHADNIRTKEEIKRQKQEHSHNHGGGSN--DQAVVAARAQGRYTTDDGYIFNASDIIE 178
BVH11 A66 121 DAAHADNIRTKEEIKRQKQEHSHNHGGGSN--DQAVVAARAQGRYTTDDGYIFNASDIIE 178
BVH11 Rx1 121 DAAHADNIRTKEEIKRQKQEHSHNHSRA---DNAAAAAAGQRYTTDDGYIFNASDIIE 177
BVH11 JNR7/87 121 DAAHADNIRTKEEIKRQKQEHSHNHSRA---DNAAAAAAGQRYTTDDGYIFNASDIIE 177
BVH11 SP63 121 DAAHADNIRTKEEIKRQKQEHSHNHSRA---DNAAAAAAGQRYTTDDGYIFNASDIIE 177
BVH11 SP64 120 DAAHADNVRTKEEINRQKQEHSQHREGGTSANDGAVAFARSQGRYTTDDGYIFNASDIIE 179

BVH11-2 SP64 178 DTGDYIVPHGDHYHYIPKNELASASELAAAEAYWNGKQGRPSSSSSSYNANPAQPRLSN 237
BVH11-2 JNR7/87 179 DTGDYIVPHGDHYHYIPKNELASASELAAAEAYWNGKQGRPSSSSSSYNANPAQPRLSN 238
BVH11-2 P4241 179 DTGDYIVPHGNHPHYIPKSDLSASELAAQAAYWNGKQGRPSSSSSSHNANPAQPRLSN 238
BVH11-2 A66 179 DTGDYIVPHGNHPHYIPKSDLSASELAAQAAYWNGKQGRPSSSSSSHNANPAQPRLSN 238
BVH11-2 WU2 179 DTGDYIVPRGNHPHYIPKSDLSASELAAQAAYWNGKQGRPSSSSSSHNANPAQPRLSN 238
BVH11-2 Rx1 178 DTGDYIVPHGDHYHYIPKSDLSASELAAQAAYWNGKQGRPSSSSSSHNANPAQPRLSN 237
BVH11 P4241 179 DTGDYIVPHGNHPHYIPKSDLSASELAAQAAYWNGKQGRPSSSSSSHNANPAQPRLSN 238
BVH11 WU2 179 DTGDYIVPHGNHPHYIPKSDLSASELAAQAAYWNGKQGRPSSSSSSHNANPAQPRLSN 238
BVH11 A66 179 DTGDYIVPHGNHPHYIPKSDLSASELAAQAAYWNGKQGRPSSSSSSHNANPAQPRLSN 238
BVH11 Rx1 178 DTGDYIVPHGDHYHYIPKSDLSASELAAQAAYWNGKQGRPSSSSSSHNANPAQPRLSN 237
BVH11 JNR7/87 178 DTGDYIVPHGDHYHYIPKNELASASELAAAEAYWNGKQGRPSSSSSSYNANPAQPRLSN 237
BVH11 SP63 178 DTGDYIVPHGNHPHYIPKSDLSASELAAQAAYWNGKQGRPSSSSSSHNANPAQPRLSN 237
BVH11 SP64 180 DTGDYIVPHGDHYHYIPKNELASASELAAAEAFSGRENLSNLRTRYRRQNSDNTPRTNWV 239

BVH11-2 SP64 238 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 285
 BVH11-2 JNR7/87 239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
 BVH11-2 P4241 239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
 BVH11-2 A66 239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
 BVH11-2 WU2 239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
 BVH11-2 Rx1 238 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 285
 BVH11 P4241 239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
 BVH11 WU2 239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
 BVH11 A66 239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
 BVH11 Rx1 238 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 285
 BVH11 JNR7/87 238 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 285
 BVH11 SP63 238 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 285
 BVH11 SP64 240 PSVSNPGTTNTNTSNNSTNSQASQSDNDISLLKQLYKLPLSRHVESDGLIFDPAQITS 299
 * * * * *

BVH11-2 SP64 286 RTARGVAVPHGNHYHFIPYEQMSELEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 345
 BVH11-2 JNR7/87 287 RTARGVAVPHGNHYHFIPYEQMSELEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 346
 BVH11-2 P4241 287 RTARGVAVPHGNHYHFIPYEQMSELEERARIIPLYRSNHWVPDSRPEQSPQ-----PS 342
 BVH11-2 A66 287 RTARGVAVPHGNHYHFIPYEQMSELEERARIIPLYRSNHWVPDSRPEQSPQ-----PS 342
 BVH11-2 WU2 287 RTARGVAVPHGNHYHFIPYEQMSELEERARIIPLYRSNHWVPDSRPEQSPQ-----PS 342
 BVH11-2 Rx1 286 RTANGVAVPHGDHYHFIPYSQSLPLEEKLARIIPLYRSNHWVPDSRPEQSPQSTPEPS 345
 BVH11 P4241 287 RTARGVAVPHGNHYHFIPYEQMSELEERARIIPLYRSNHWVPDSRPEQSPQ-----PS 342
 BVH11 WU2 287 RTARGVAVPHGNHYHFIPYEQMSELEERARIIPLYRSNHWVPDSRPEQSPQ-----PS 342
 BVH11 A66 287 RTARGVAVPHGNHYHFIPYEQMSELEERARIIPLYRSNHWVPDSRPEQSPQ-----PS 342
 BVH11 Rx1 286 RTANGVAVPHGDHYHFIPYSQSLPLEEKLARIIPLYRSNHWVPDSRPEQSPQSTPEPS 345
 BVH11 JNR7/87 286 RTARGVAVPHGNHYHFIPYEQMSELEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 345
 BVH11 SP63 286 RTARGVAVPHGNHYHFIPYSQSLPLEEKLARIIPLYRSNHWVPDSRPEQSPQSTPEPS 345
 BVH11 SP64 300 RTARGVAVPHGNHYHFIPYEQMSELEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 359
 * * * * *

BVH11-2 SP64 346 PSLQPAPNPQPAPSNPIDKLVKEAVRKVG DG YVFEENGVSRYIPAKOLSAETAAGIDSK 405
 BVH11-2 JNR7/87 347 PSLQPAPNPQPAPSNPIDKLVKEAVRKVG DG YVFEENGVSRYIPAKOLSAETAAGIDSK 406
 BVH11-2 P4241 343 PSLQPAPNPQPAPSNPIDKLVKEAVRKVG DG YVFEENGVSRYIPAKOLSAETAAGIDSK 402
 BVH11-2 A66 343 PSLQPAPNPQPAPSNPIDKLVKEAVRKVG DG YVFEENGVSRYIPAKOLSAETAAGIDSK 402
 BVH11-2 WU2 343 PSLQPAPNPQPAPSNPIDKLVKEAVRKVG DG YVFEENGVSRYIPAKOLSAETAAGIDSK 402
 BVH11-2 Rx1 346 PSLQPAPNPQPAPSNPIDKLVKEAVRKVG DG YVFEENGVSRYIPAKOLSAETAAGIDSK 405
 BVH11 P4241 343 PSLQPAPNPQPAPSNPIDKLVKEAVRKVG DG YVFEENGVSRYIPAKOLSAETAAGIDSK 402
 BVH11 WU2 343 PSLQPAPNPQPAPSNPIDKLVKEAVRKVG DG YVFEENGVSRYIPAKOLSAETAAGIDSK 402
 BVH11 A66 343 PSLQPAPNPQPAPSNPIDKLVKEAVRKVG DG YVFEENGVSRYIPAKOLSAETAAGIDSK 402
 BVH11 Rx1 346 PSLQPAPNPQPAPSNPIDKLVKEAVRKVG DG YVFEENGVSRYIPAKOLSAETAAGIDSK 405
 BVH11 JNR7/87 346 PSLQPAPNPQPAPSNPIDKLVKEAVRKVG DG YVFEENGVSRYIPAKOLSAETAAGIDSK 399
 BVH11 SP63 346 PSLQPAPNPQPAPSNPIDKLVKEAVRKVG DG YVFEENGVSRYIPAKOLSAETAAGIDSK 405
 BVH11 SP64 360 PSLQPAPNPQPAPSNPIDKLVKEAVRKVG DG YVFEENGVSRYIPAKOLSAETAAGIDSK 419
 * * * * *

BVH11-2 SP64 406 LAKQESLSHKLGA KKTDL PSSDREFY NKAYD LLARIHQD LLDNKG RQVDFEALDNLLERL 465
 BVH11-2 JNR7/87 407 LAKQESLSHKLGA KKTDL PSSDREFY NKAYD LLARIHQD LLDNKG RQVDFEALDNLLERL 466
 BVH11-2 P4241 403 LAKQESLSHKLGT KKTDL PSSDREFY NKAYD LLARIHQD LLDNKG RQVDFEALDNLLERL 462
 BVH11-2 A66 403 LAKQESLSHKLGT KKTDL PSSDREFY NKAYD LLARIHQD LLDNKG RQVDFEALDNLLERL 462
 BVH11-2 WU2 403 LAKQESLSHKLGT KKTDL PSSDREFY NKAYD LLARIHQD LLDNKG RQVDFEALDNLLERL 462
 BVH11-2 Rx1 406 LAKQESLSHKLGA KKTDL PSSDREFY NKAYD LLARIHQD LLDNKG RQVDFEALDNLLERL 465
 BVH11 P4241 403 LAKQESLSHKLGT KKTDL PSSDREFY NKAYD LLARIHQD LLDNKG RQVDFEALDNLLERL 462
 BVH11 WU2 403 LAKQESLSHKLGT KKTDL PSSDREFY NKAYD LLARIHQD LLDNKG RQVDFEALDNLLERL 462
 BVH11 A66 403 LAKQESLSHKLGT KKTDL PSSDREFY NKAYD LLARIHQD LLDNKG RQVDFEALDNLLERL 462
 BVH11 Rx1 406 LAKQESLSHKLGA KKTDL PSSDREFY NKAYD LLARIHQD LLDNKG RQVDFEALDNLLERL 465
 BVH11 JNR7/87 400 LAKQESLSHKLGA KKTDL PSSDREFY NKAYD LLARIHQD LLDNKG RQVDFEALDNLLERL 459
 BVH11 SP63 406 LAKQESLSHKLGA KKTDL PSSDREFY NKAYD LLARIHQD LLDNKG RQVDFEALDNLLERL 465
 BVH11 SP64 420 LAKQESLSHKLGA KKTDL PSSDREFY NKAYD LLARIHQD LLDNKG RQVDFEALDNLLERL 479
 * * * * *

BVH11-2 SP64 466 KDVSSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 525
BVH11-2 JNR7/87 467 KDVPSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 526
BVH11-2 P4241 463 KDVSSDKVKLVVEDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 522
BVH11-2 A66 463 KDVSSDKVKLVVEDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 522
BVH11-2 WU2 463 KDVSSDKVKLVVEDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 522
BVH11-2 Rx1 466 KDVSSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 525
BVH11 P4241 463 KDVSSDKVKLVVEDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 522
BVH11 WU2 463 KDVSSDKVKLVVEDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 522
BVH11 A66 463 KDVSSDKVKLVVEDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 522
BVH11 Rx1 466 KDVSSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 525
BVH11 JNR7/87 460 KDVSSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 519
BVH11 SP63 466 KDVPSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 525
BVH11 SP64 480 KDVSSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 539

BVH11-2 SP64 526 RDITSDEGDAYVTPHMTSHWIKKDSLSAERAAAQAYAKEKGLTPPSTDHQDSGNTSEAK 585
BVH11-2 JNR7/87 527 RDITSDEGDAYVTPHMTSHWIKKDSLSAERAAAQAYAKEKGLTPPSTDHQDSGNTSEAK 586
BVH11-2 P4241 523 RDITSDEGDAYVTPHMTSHWIKKDSLSAERAAAQAYAKEKGLTPPSTDHQDSGNTSEAK 582
BVH11-2 A66 523 RDITSDEGDAYVTPHMTSHWIKKDSLSAERAAAQAYAKEKGLTPPSTDHQDSGNTSEAK 582
BVH11-2 WU2 523 RDITSDEGDAYVTPHMTSHWIKKDSLSAERAAAQAYAKEKGLTPPSTDHQDSGNTSEAK 582
BVH11-2 Rx1 526 RDITSDEGDAYVTPHMTSHWIKKDSLSAERAAAQAYAKEKGLTPPSTDHQDSGNTSEAK 585
BVH11 P4241 523 RDITSDEGDAYVTPHMTSHWIKKDSLSAERAAAQAYAKEKGLTPPSTDHQDSGNTSEAK 582
BVH11 WU2 523 RDITSDEGDAYVTPHMTSHWIKKDSLSAERAAAQAYAKEKGLTPPSTDHQDSGNTSEAK 582
BVH11 A66 523 RDITSDEGDAYVTPHMTSHWIKKDSLSAERAAAQAYAKEKGLTPPSTDHQDSGNTSEAK 582
BVH11 Rx1 526 RDITSDEGDAYVTPHMTSHWIKKDSLSAERAAAQAYAKEKGLTPPSTDHQDSGNTSEAK 585
BVH11 JNR7/87 520 RDITSDEGDAYVTPHMTSHWIKKDSLSAERAAAQAYAKEKGLTPPSTDHQDSGNTSEAK 579
BVH11 SP63 526 RDITSDEGDAYVTPHMTSHWIKKDSLSAERAAAQAYAKEKGLTPPSTDHQDSGNTSEAK 585
BVH11 SP64 540 RDITSDEGDAYVTPHMTSHWIKKDSLSAERAAAQAYAKEKGLTPPSTDHQDSGNTSEAK 599

BVH11-2 SP64 586 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 645
BVH11-2 JNR7/87 587 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 646
BVH11-2 P4241 583 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11-2 A66 583 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11-2 WU2 583 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11-2 Rx1 586 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 645
BVH11 P4241 583 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11 WU2 583 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11 A66 583 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11 Rx1 586 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 645
BVH11 JNR7/87 580 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 639
BVH11 SP63 586 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 645
BVH11 SP64 600 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 659

BVH11-2 SP64 646 GYSLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKKN-----ADQDSK 690
BVH11-2 JNR7/87 647 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKKN-----VDQDSK 691
BVH11-2 P4241 643 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKKN-----ADQDSK 687
BVH11-2 A66 643 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKKN-----ADQDSK 687
BVH11-2 WU2 643 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKKN-----ADQDSK 687
BVH11-2 Rx1 646 GYSLEDLLATVKYVVEHPNERPHSDNGFGNASDHVQRNKGQADTNTQTEKPNEEKPQTEK 705
BVH11 P4241 643 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKKN-----ADQDSK 687
BVH11 WU2 643 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKKN-----ADQDSK 687
BVH11 A66 643 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKKN-----ADQDSK 687
BVH11 Rx1 646 GYSLEDLLATVKYVVEHPNERPHSDNGFGNASDHVQRNKN-----NGQ 687
BVH11 JNR7/87 640 GYSLEDLLATVKYVVEHPNERPHSDNGFGNASDHVQRNKN-----NGQ 681
BVH11 SP63 646 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVQRNKN-----NGQ 687
BVH11 SP64 660 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVQRNKN-----NGQ 701

FIGURE 12

BVH11-2 SP64	BVH11 SP63	BVH11 JNR. 7/87	BVH11-2 JNR. 7/87	BVH11 WU2	BVH11-2 WU2	BVH11 A66	BVH11-2 A66	BVH11 P4241	BVH11-2 P4241	BVH11 Rx-1	BVH11-2 Rx-1
I 81%	I 88%	I 88%	I 82%	I 80%	I 80%	I 80%	I 80%	I 80%	I 80%	I 88%	I 81%
S 86%	S 90%	S 91%	S 87%	S 85%	S 85%	S 85%	S 85%	S 85%	S 85%	S 91%	S 85%
	I 87%	I 87%	I 98%	I 96%	I 96%	I 95%	I 96%	I 95%	I 96%	I 87%	I 94%
	S 90%	S 90%	S 98%	S 97%	S 97%	S 96%	S 97%	S 96%	S 97%	S 90%	S 95%
		I 96%	I 88%	I 87%	I 87%	I 88%	I 87%	I 88%	I 87%	I 97%	I 89%
		S 96%	S 91%	S 91%	S 90%	S 91%	S 90%	S 91%	S 90%	S 97%	S 91%
			I 87%	I 87%	I 86%	I 87%	I 86%	I 87%	I 86%	I 96%	I 88%
			S 90%	S 91%	S 90%	S 91%	S 90%	S 91%	S 90%	S 96%	S 90%
				I 96%	I 97%	I 96%	I 97%	I 96%	I 97%	I 87%	I 94%
				S 97%	S 98%	S 97%	S 98%	S 97%	S 98%	S 90%	S 95%
					I 98%	I 92%	I 98%	I 99%	I 98%	I 87%	I 92%
					S 98%	S 94%	S 98%	S 99%	S 98%	S 91%	S 94%
						I 98%	I 99%	I 98%	I 99%	I 86%	I 93%
						S 98%	S 99%	S 98%	S 99%	S 90%	S 95%
							I 99%	I 100%	I 99%	I 87%	I 92%
							S 99%		S 99%	S 91%	S 94%
								I 99%	I 99%	I 86%	I 93%
								S 99%	S 99%	S 90%	S 95%
									I 99%	I 87%	I 92%
									S 99%	S 91%	S 94%
										I 86%	I 93%
										S 90%	S 95%
											I 91%
											S 92%

FIGURE 13

AATTCCTTGT	CGGGTAAGTT	CCGACCCGCA	CGAAAGGCGT	AATGATTTGG	GCACTGTCTC	60
AACGAGAGAC	TCGGTGAAAT	TTTAGTACCT	GTGAAGATGC	AGGTTACCCG	CGACAGGACG	120
GAAAGACCCC	ATGGAGCTTT	ACTGCAGTTT	GATATTGAGT	GTCTGTACCA	CATGTACAGG	180
ATAGGTAGGA	GTCTAAGAGA	TCGGGACGCC	AGTTTCGAAG	GAGACGCTGT	TGGGATACTA	240
CCCTTGTGTT	ATGGCCACTC	TAACCCAGAT	AGGTGATCCC	TATCGGAGAC	AGTGTCTGAC	300
GGGCAGTTTG	ACTGGGGCGG	TCGCCTCCTA	AAAGGTAACG	GAGGCGCCCA	AAGGTTCCCT	360
CAGAATGGTT	GGAAATCATT	CGCAGAGTGT	AAAGGTATAA	GGGAGCTTGA	CTGCGAGAGC	420
TACAATCGA	GCAGGGACGA	AAGTCGGGCT	TAGTGATCCG	GTGGTTCCCT	ATGGAAGGGC	480
CATCGCTCAA	CGGATAAAAG	CTACCCTGGG	GATAACAGGC	TTATCTCCCC	CAAGAGTTCA	540
CATCGACGGG	GAGGTTTGGC	ACCTCGATGT	CGGCTCGTCG	CATCCTGGGG	CTGTAGTCGG	600
TCCCAAGGGT	TGGGCTGTTC	GCCCATTAAG	GCGGCACGCG	AGCTGGGTTC	AGAACGTCGT	660
GAGACAGTTC	GGTCCCTATC	CGTCGCGGGC	GTAGGAAATT	TGAGAGGATC	TGCTCCTAGT	720
ACGAGAGGAC	CAGAGTGGAC	TTACCGCTGG	TGTACCAGTT	GTCTTGCCAA	AGGCATCGCT	780
GGGTAGCTAT	GTAGGGAAGG	GATAAACGCT	GAAAGCATCT	AAGTGTGAAA	CCCACCTCAA	840
GATGAGATTT	CCCATGATTA	TATATCAGTA	AGAGCCCTGA	GAGATGATCA	GGTAGATAGG	900
TTAGAAGTGG	AAGTGTGGCG	ACACATGTAG	CGGACTAATA	CTAATAGCTC	GAGGACTTAT	960
CCAAAGTAAC	TGAGAATATG	AAAGCGAACG	GTTCCTTAA	ATTGAATAGA	TATTCAATTT	1020
TGAGTAGGTA	TTACTCAGAG	TTAAGTGACG	ATAGCCTAGG	AGATACACCT	GTACCCATGC	1080
CGAACACAGA	AGTTAAGCCC	TAGAACGCCG	GAAGTAGTTG	GGGGTTGCC	CCTGTGAGAT	1140
AGGGAGTCG	CTTAGCTCTA	GGGAGTTTAG	CTCAGCTGGG	AGAGCATCTG	CCTTACAAGC	1200
AGAGGTCAG	CGGTTTCGATC	CCGTAACTC	CCAAAGGTCC	CGTAGTGTAG	CGGTTATCAC	1260
GTCCGCCCTGT	CACGGCGAAG	ATCGCGGGTT	CGATTCCCGT	CGGGACCGTT	TAAGGTAACG	1320
CAAGTTATTT	TAGACTCGTT	AGCTCAGTTG	GTAGAGCAAT	TGACTTTTAA	TCAATGGGTC	1380
ACTGGTTCGA	GCCAGTACG	GGTCATATAT	GCGGGTTTGG	CGGAATTCTA	ATCTCTTTGA	1440
AATCATCTTC	TCTCACTTTC	CAAACTCTA	TTACCTCTTA	TTATACCACA	TTCAATCTT	1500
CAACTTCCCA	GTAATATAAG	CACCTCTGGC	GAAAGAAGTT	TCAATGTCCT	AAAGTAATAA	1560
GTGAATCCAA	TTCAAGAACT	CCAAGAACAA	AAGAAACATC	TGGTGTCA	AGTATTGGAT	1620
GGCACAGAGT	CACGTGGTAG	TCTGACCCTA	GCAGAAATTT	TAAATAGTAA	ACTATTTACT	1680
GGTTAATTAA	ATGGTTAAAT	AACCGGTTTA	GAAAACTATT	TAATAAAGTA	AAAGAAGTTG	1740
AGAAAAAAT	TCATCATTTA	TTGAAATGAG	GGATTTATGA	AATTTAGTAA	AAAATATATA	1800
GCAGCTGGAT	CAGCTGTTAT	CGTATCCTTG	AGTCTATGTG	CCTATGCACT	AAACCAAGCAT	1860
CGTTTCGCAGG	AAAATAAGGA	CAATAATCGT	GTCTCTTATG	TGGATGGCAG	CCAGTCAAGT	1920
CAGAAAAGTG	AAAACCTTAC	ACCAGACCAG	GTTAGCCAGA	AAGAAGGAAT	TCAGGCTGAG	1980
CAAATTGTAA	TCAAAATTAC	AGATCAGGGC	TATGTAACGT	CACACGGTGA	CCACTATCAT	2040
TACTATAATG	GGAAAGTTCC	TTATGATGCC	CTCTTTAGTG	AAGAACTCTT	GATGAAGGAT	2100
CCAACTATC	AACTTAAAGA	CGCTGATATT	GTCAATGAAG	TCAAGGGTGG	TTATATCATC	2160
AAGGTCGATG	GAAAATATTA	TGTCTACCTG	AAAGATGCAG	CTCATGCTGA	TAATGTTCTGA	2220
ACTAAAGATG	AAATCAATCG	TCAAAAACAA	GAACATGTCA	AAGATAATGA	GAAGGTTAAC	2280
TCTAATGTTG	CTGTAGCAAG	GTCTCAGGGA	CGATATACGA	CAAATGATGG	TTATGTCTTT	2340
AATCCAGCTG	ATATTATCGA	AGATACGGGT	AATGCTTATA	TCGTTCTCTA	TGGAGGTCAC	2400
TATCACTACA	TTCCCAAAAG	CGATTTATCT	GCTAGTGAAT	TAGCAGCAGC	TAAAGCACAT	2460
CTGGCTGGAA	AAAATATGCA	ACCGAGTCAG	TTAAGCTATT	CTTCAACAGC	TAGTGACAAT	2520
AACACGCAAT	CTGTAGCAAA	AGGATCAACT	AGCAAGCCAG	CAAATAAATC	TGAAAATCTC	2580
CAGAGTCTTT	TGAAGGAACT	CTATGATTCA	CCTAGCGCCC	AACGTTACAG	TGAATCAGAT	2640
GGCCTGGTCT	TTGACCCTGC	TAAGATTATC	AGTCGTACAC	CAAATGGAGT	TGCGATTCCG	2700
CATGGCGACC	ATTACCACTT	TATTCCTTAC	AGCAAGCTTT	CTGCTTTAGA	AGAAAAGATT	2760
GCCAGAATGG	TGCCTATCAG	TGGAACCTGGT	TCTACAGTTT	CTACAAATGC	AAAACCTAAT	2820
GAAGTAGTGT	CTAGTCTAGG	CAGTCTTTCA	AGCAATCCTT	CTTCTTTAAC	GACAAGTAAG	2880
GAGCTCTCTT	CAGCATCTGA	TGGTTATATT	TTTAATCCAA	AAGATATCGT	TGAAGAAACG	2940
GCTACAGOTT	ATATTGTAAG	ACATGGTGAT	CATTTCCATT	ACATTCCAAA	ATCAAATCAA	3000
ATTGGGCAAC	CGACTCTTCC	AAACAATAGT	CTAGCAACAC	CTTCTCCATC	TCTTCCAATC	3060
AATCCAGGAA	CTTCACATGA	GAAACATGAA	GAAGATGGAT	ACGGATTTGA	TGCTAATCGT	3120
ATTCTCGCTG	AAGATGAATC	AGGTTTTGTC	ATGAGTCACG	GAGACCACAA	TCATTATTTT	3180
TTCAAGAAGG	ACTTGACAGA	AGAGCAAATT	AAGGCTCGCG	AAAAACATTT	AGAGGAAGTT	3240
AAAAGTAGTC	ATAATGGATT	AGATTCTTTG	TACTCTCATG	AACAGGATTA	TCCAGGTAAT	3300
GCCAAAGAAA	TGAAAGATTT	AGATAAAAAA	ATCGAAGAAA	AAATTGCTGG	CATTATGAAA	3360

CAATATGGTG	TCAAACGTGA	AAGTATTGTC	GTGAATAAAG	AAAAAAATGC	GATTATTTAT	3420
CCGCATGGAG	ATCACCATCA	TGCAGATCCG	ATTGATGAAC	ATAAACCCGT	TGGAATTGGT	3480
CATTCTCACA	GTAACATGA	ACTGTTTAAA	CCCGAAGAAG	GAGTTGCTAA	AAAAGAAGGG	3540
AATAAAGTTT	ATACTGGAGA	AGAATTAACG	AATGTTGTGA	ATTTGTTAAA	AAATAGTACG	3600
TTTAATAATC	AAAACTTTAC	TCTAGCCAAT	GGTCAAAAAC	GCGTTTCTTT	TAGTTTTCCG	3660
CCTGAATTGG	AGAAAAAATT	AGGTATCAAT	ATGCTAGTAA	AATTAATAAC	ACCAGATGGA	3720
AAAGTATTGG	AGAAAGTATC	TGGTAAAGTA	TTTGGAGAAG	GAGTAGGGAA	TATTGCAAAC	3780
TTTGAATTAG	ATCAACCTTA	TTTACCAGGA	CAAACATTTA	AGTATACTAT	CGCTTCAAAA	3840
GATTATCCAG	AAGTAAGTTA	TGATGGTACA	TTTACAGTTC	CAACCTCTTT	AGCTTACAAA	3900
ATGGCCAGTC	AAACGATTTT	CTATCCTTTC	CATGCAGGGG	ATACTTATTT	AAGAGTGAAC	3960
CCTCAATTTG	CAGTGCCTAA	AGGAACTGAT	GCTTTAGTCA	GAGTGTGTTA	TGAATTTTCA	4020
GGAAATGCTT	ATTTAGAAAA	TAACATATAA	GTTGGTGAAA	TCAAATTACC	GATTCCGAAA	4080
TTAAACCAAG	GAACAACCAG	AACGGCCGGA	AATAAAATTC	CTGTAACCTT	CATGGCAAAT	4140
GCTTATTGGG	ACAATCAATC	GACTTATATT	GTGGAAGTAC	CTATCTTGGA	AAAAGAAAAAT	4200
CAAACTGATA	AACCAAGTAT	TCTACCACAA	TTTAAAAGGA	ATAAAGCACA	AGAAAACTCA	4260
AAACTTGATG	AAAAGGTAGA	AGAACCAAAG	ACTAGTGAGA	AGGTAGAAAA	AGAAAACTT	4320
TCTGAAACTG	GGAAATAGTAC	TAGTAATTCA	ACGTTAGAAG	AAGTTCCTAC	AGTGGATCCT	4380
GTACAAGAAA	AAGTAGCAAA	ATTTGCTGAA	AGTTATGGGA	TGAAGCTAGA	AAATGTCTTG	4440
TTTAATATGG	ACGGAACAAT	TGAATTATAT	TTACCATCAG	GAGAAGTCAT	TAAAAAGAAAT	4500
ATGGCAGATT	TTACAGGAGA	AGCACCTCAA	GGAAATGGTG	AAAATAAACC	ATCTGAAAAAT	4560
GGAAAAGTAT	CTACTGGAAC	AGTTGAGAAC	CAACCAACAG	AAAATAAACC	AGCAGATTCT	4620
TTACCAGAGG	CACCAAACGA	AAAACCTGTA	AAACCAGAAA	ACTCAACGGA	TAATGGAATG	4680
TTGAATCCAG	AAGGGAATGT	GGGGAGTGAC	CCTATGTTAG	ATCCAGCATT	AGAGGAAGCT	4740
CCAGCAGTAG	ATCCTGTACA	AGAAAAATTA	GAAAAATTTA	CAGCTAGTTA	CGGATTAGGC	4800
TTAGATAGTG	TTATATTCAA	TATGGATGGA	ACGATTGAAT	TAAGATTGCC	AAGTGGAGAA	4860
GTGATAAAAA	AGAATTTATC	TGATTTTCATA	GCGTAAGGAA	TAGCAGTAGA	AAAAGTCTGA	4920
ATCAAAAAATG	AAGTTCTCTC	AAAAGTTAGA	AATAAACTC	TGACTTTGGG	AGAATTTTCAT	4980
TTTATTATTA	ATATATAAAA	TTTCTTGACA	TACAACCTTA	AAAGAGGTGG	AATATTTACT	5040
AGTTAATT	(SEQ ID NO : 11)					5048

FIGURE 14

CAGAGATCTT	AGTGAATCAA	ATATACTTAA	GAAAAGAGGA	AAGAATGAAA	ATCAATAAAA	60
AATATCTAGC	TGGGTCAGTA	GCTACACTTG	TTTTAAGTGT	CTGTGCTTAT	GAAGTGGTT	120
TGCATCAAGC	TCAAACCTGTA	AAAGAAAATA	ATCGTGTTTC	CTATATAGAT	GGAAAACAAG	180
CGACGCAAAA	AACGGAGAAT	TTGACTCCTG	ATGAGGTTAG	CAAGCGTGAA	GGAATCAACG	240
CCGAACAAAT	CGTCATCAAG	ATTACGGATC	AAGGTTATGT	GACCTCTCAT	GGAGACCATT	300
ATCATTACTA	TAATGGCAAG	GTCCCTTATG	ATGCCATCAT	CAGTGAAGAG	CTCCTCATGA	360
AAGATCCGAA	TTATCAGTTG	AAGGATTGAG	ACATTGTCAA	TGAAATCAAG	GGTGGTTATG	420
TCATTAAGGT	AAACGGTAAA	TACTATGTTT	ACCTTAAGGA	TGCAGCTCAT	GCGGATAATG	480
TCCGTACAAA	AGAAGAAATC	AATCGGCAAA	AACAAGAACA	TAGTCAGCAT	CGTGAAGGAG	540
GGACTTCAGC	AAACGATGGT	GCGGTAGCCT	TTGCACGTTT	ACAGGGACGC	TACACCACAG	600
ATGATGGTTA	TATCTTCAAT	GCATCTGATA	TCATCGAAGA	TACGGGCGAT	GCCTATATCG	660
TTCCTCATGG	AGATCATTAC	CATTACATTC	CTAAGAATGA	GTTATCAGCT	AGCGAGTTGG	720
CTGCTGCAGA	AGCCTTCCTA	TCTGGTCGGG	AAAATCTGTC	AAATTTAAGA	ACCTATCGCC	780
GACAAAATAG	CGATAACACT	CCAAGAACAA	ACTGGGTACC	TTCTGTAAAG	AATCCAGGAA	840
CTACAAATAC	TAACACAAGC	AACAACAGCA	ACACTAACAG	TCAAGCAAGT	CAAAGTAATG	900
ACATTGATAG	TCTCTTGAAA	CAGCTCTACA	AACGCTTTT	GAGTCAACGC	CATGTAGAAT	960
CTGATGGCCT	TATTTTCGAC	CCAGCGCAAA	TCACAAGTCG	AACCGCCAGA	GGTGTAGCTG	1020
TCCCTCATGG	TAACCATTAC	CACCTTATCC	CTTATGAACA	AATGTCTGAA	TTGGAAAAAC	1080
GAATTGCTCG	TATTATTCCC	CTTCGTTATC	GTTCAAACCA	TTGGGTACCA	GATTCAAGAC	1140
CAGAAGAACC	AAGTCCACAA	CCGACTCCAG	AACCTAGTCC	AAGTCCGCAA	CCTGCACCAA	1200
ATCCTCAACC	AGCTCCAAGC	AATCCAATTG	ATGGAATAAT	GGTCAAAGAA	GCTGTTCCGA	1260
AAGTAGGCGA	TGGTTATGTC	TTTGAGGAGA	ATGGAGTTTC	TGCTTATATC	CCAGCCAAGA	1320
ATCTTTCAGC	AGAAACAGCA	GCAGGCATTG	ATAGCAAACCT	GGCCAAGCAG	GAAAGTTTAT	1380
CTCATAAGCT	AGGAGCTAAG	AAAACCTGACC	TCCCCTCTAG	TGATCGAGAA	TTTACAATA	1440
AGGCTTATGA	CTTACTAGCA	AGAATTCACC	AAGATTTACT	TGATAATAAA	GGTCGACAAG	1500
TTGATTTTGA	GGCTTTGGAT	AACCTGTTGG	AACGACTCAA	GGATGTCTCA	AGTGATAAAG	1560
TCAAGTTAGT	GGATGATATT	CTTGCCTTCT	TAGCTCCGAT	TGCTCATCCA	GAACGTTTAT	1620
GAAAACCAAA	TGCGCAAATT	ACCTACACTG	ATGATGAGAT	TCAAGTAGCC	AAGTTGGCAG	1680
GCAAGTACAC	AACAGAAGAC	GGTTATATCT	TTGATCCTCG	TGATATAACC	AGTGATGAGG	1740
GGGATGCCTA	TGTAACCTCA	CATATGACCC	ATAGCCACTG	GATTAAAAAA	GATAGTTTGT	1800
CTGAAGCTGA	GAGAGCGGCA	GCCCAGGCTT	ATGCTAAAGA	GAAAGGTTTG	ACCCCTCCTT	1860
CGACAGACCA	TCAGGATTCA	GGAAATACTG	AGGCAAAAGG	AGCAGAAGCT	ATCTACAACC	1920
GCGTGAAAGC	AGCTAAGAAG	GTGCCACTTG	ATCGTATGCC	TTACAATCTT	CAATATACTG	1980
TAGAAGTCAA	AAACGGTAGT	TTAATCATAC	CTCATTATGA	CCATTACCAT	AACATCAAAT	2040
TTGAGTGTTT	TGACGAAGGC	CTTTATGAGG	CACCTAAGGG	GTATACTCTT	GAGGATCTTT	2100
TGGCGACTGT	CAAGTACTAT	GTCGAACATC	CAAACGAACG	TCCGCATTCA	GATAATGGTT	2160
TTGGTAACGC	TAGCGACCAT	GTTCAAAGAA	ACAAAATGG	TCAAGCTGAT	ACCAATCAAA	2220
CGGAAAAACC	AAGCGAGGAG	AAACCTCAGA	CAGAAAAACC	TGAGGAAGAA	ACCCCTCGAG	2280
AAGAGAAACC	ACAAAGCGAG	AAACCAGAGT	CTCCAAAACC	AACAGAGGAA	CCAGAAGAAG	2340
AATCACCAGA	GGAATCAGAA	GAACCTCAGG	TCGAGACTGA	AAAGGTTGAA	GAAAAACTGA	2400
GAGAGGCTGA	AGATTTACTT	GGAAAAATCC	AGGATCCAAT	TATCAAGTCC	AATGCCAAAG	2460
AGACTCTCAC	AGGATTAAAA	AATAATTTAC	TATTTGGCAC	CCAGGACAAC	AATACTATTA	2520
TGGCAGAAGC	TGAAAACTA	TTGGCTTTAT	TAAAGGAGAG	TAAGTAAAGG	TAGCAGCATT	2580
TTCTAACTCC	TAAAAACAGG	ATAGGAGAAC	GGGAAAAACG	AAAATGAGAG	CAGAATGTGA	2640
GTTCTAG	(SED ID NO : 12)					2647

FIGURE 15

GGGTCTTAAA	ACTCTGAATC	CTTTAGAGGC	AGACCCACAA	AAATGACAAGA	CCTATTTAGA	60
AAATCTGGAA	GAAAATATGA	GTGTTCTAGC	AGAAGAATTA	AAGTGAGGAA	AGAATGAAAA	120
TCAATAAAAA	ATATCTAGCA	GGTTCAGTGG	CAGTCCTTGC	CCTAAGTGTT	TGTTCCCTATG	180
AACTTGGTCG	TCACCAAGCT	GGTCAGGTTA	AGAAAGAGTC	TAATCGAGTT	TCTTATATAG	240
ATGGTGATCA	GGCTGGTCAA	AAGGCAGAAA	ATTTGACACC	AGATGAAGTC	AGTAAGAGAG	300
AGGGGATCAA	CGCCGAACAA	ATTGTTATCA	AGATTACGGA	TCAAGGTTAT	GTGACCTCTC	360
ATGGAGACCA	TTATCATTAC	TATAATGGCA	AGGTTCCCTTA	TGATGCCATC	ATCAGTGAAG	420
AACTTCTCAT	GAAAGATCCG	AATTATCAGT	TGAAGGATTC	AGACATTGTC	AATGAAATCA	480
AGGGTGGCTA	TGTGATTAAG	GTAGACGGAA	AATACTATGT	TTACCTTAAA	GATCGGGCCC	540
ATGCGGACAA	TATTCGGACA	AAAGAAGAGA	TTAAACGTCA	GAAGCAGGAA	CACAGTCATA	600
ATCATAACTC	AAGAGCAGAT	AATGCTGTTG	CTGCAGCCAG	AGCCCAAGGA	CGTTATACAA	660
CGGATGATGG	GTATATCTTC	AATGCATCTG	ATATCATTGA	GGACACGGGT	GATGCTTATA	720
TCGTTCCCTCA	CGGCGACCAT	TACCATTACA	TTCTTAAGAA	TGAGTTATCA	GCTAGCGAGT	780
TAGCTGCTGC	AGAAGCCTAT	TGGAATGGGA	AGCAGGGATC	TCGTCCTTCT	TCAAGTTCTA	840
GTTATAATGC	AAATCCAGTT	CAACCAAGAT	TGTCAGAGAA	CCACAATCTG	ACTGTCACTC	900
CAACTTATCA	TCAAAATCAA	GGGGAATAACA	TTTCAAGCCT	TTTACGTGAA	TTGTATGCTA	960
AACCCTTATC	AGAACGCCAT	GTAGAATCTG	ATGGCCTTAT	TTTCGACCCA	GCGCAAATCA	1020
CAAGTCGAAC	CGCCAGAGGT	GTAGCTGTCC	CTCATGGTAA	CCATTACCAC	TTTATCCCTT	1080
ATGAACAAAT	GTCTGAATTG	GAAAAACGAA	TTGCTCGTAT	TATTTCCCTT	CGTTATCGTT	1140
CAAACCATTG	GGTACCAGAT	TCAAGACCAG	AACAACCAAG	TCCACAATCG	ACTCCGGAAC	1200
CTAGTCCAAG	TCTGCAACCT	GCACCAAAATC	CTCAACCAGC	TCCAAGCAAT	CCAATTGATG	1260
AGAAATTGGT	CAAAGAAGCT	GTTTCGAAAAG	TAGGCGATGG	TTATGTCTTT	GAGGAGAAATG	1320
GAGTTTCTCG	TTATATCCCA	GCCAAGGATC	TTTCAGCAGA	AACAGCAGCA	GGCATTGATA	1380
GCAAACCTGGC	CAAGCAGGAA	AGTTTATCTC	ATAAGCTAGG	AGCTAAGAAA	ACTGACCTCC	1440
CATCTAGTGA	TCGAGAATT	TACAATAAGG	CTTATGACTT	ACTAGCAAGA	ATTCACCAAG	1500
ATTTACTTGA	TAATAAAGGT	CGACAAGTTG	ATTTGAGGT	TTTGGATAAC	CTGTTGGAAC	1560
GACTCAAGGA	TGTCTCAAGT	GATAAAGTCA	AGTTAGTGGA	TGATATTCTT	GCCTTCTTAG	1620
CTCCGATTCTG	TCATCCAGAA	CGTTTAGGAA	AACCAAAATG	GCAAATTACC	TACACTGATG	1680
ATGAGATTCA	AGTAGCCAAG	TTGGCAGGCA	AGTACACAAC	AGAAGACGGT	TATATCTTTG	1740
ATCCTCGTGA	TATAACCAGT	GATGAGGGGG	ATGCCTATGT	AACTCCACAT	ATGACCCATA	1800
GCCACTGGAT	TAAAAAAGAT	AGTTTGCTCTG	AAGCTGAGAG	AGCGGCAGCC	CAGGCTTATG	1860
CTAAAGAGAA	AGGTTTGACC	CCTCCTTCGA	CAGACCACCA	GGATTACGGA	AATACTGAGG	1920
CAAAAGGAGC	AGAAGCTATC	TACAACCGCG	TGAAAGCAGC	TAAGAAGGTG	CCACTTGATC	1980
GTATGCCTTA	CAATCTTCAA	TATACTGTAG	AAGTCAAAAA	CGGTAGTTTA	ATCATACCTC	2040
ATTATGACCA	TTACCATAAC	ATCAAATTTG	AGTGGTTTGA	CGAAGGCCCT	TATGAGGCAC	2100
CTAAGGGGTA	TAGTCTTGAG	GATCTTTTGG	CGACTGTCAA	GTACTATGTC	GAACATCCAA	2160
ACGAACGTCC	GCATTAGAT	AATGGTTTTG	GTAACGCTAG	TGACCATGTT	CGTAAAAATA	2220
AGGCAGACCA	AGATAGTAAA	CCTGATGAAG	ATAAGGAACA	TGATGAAGTA	AGTGAGCCAA	2280
CTCACCCTGA	ATCTGATGAA	AAAGAGAATC	ACGCTGGTTT	AAATCCTTCA	GCAGATAATC	2340
TTTATAAACC	AAGCACTGAT	ACGGAAGAGA	CAGAGGAAGA	AGCTGAAGAT	ACCACAGATG	2400
AGGCTGAAAT	TCCTCAAGTA	GAGAATTCTG	TTATTAACGC	TAAGATAGCA	GATGCGGAGG	2460
CCTTGCTAGA	AAAAGTAACA	GATCCTAGTA	TTAGACAAAA	TGCTATGGAG	ACATTGACTG	2520
GTCTAAAAAG	TAGTCTTCTT	CTCGGAACGA	AAGATAATAA	CACTATTTCA	GCAGAAGTAG	2580
ATAGTCTCTT	GGCTTTGTGA	AAAGAAAGTC	AACCGGCTCC	TATACAGTAG	TAAAATGAA	2639

(SEQ ID NO : 13)

FIGURE 16

MKINKKYL	AG	SVAVLALSVC	SYELGRHQAG	QVKKESNRVS	YIDGDQAGQK	50
AENLTPDEV	S	KREGINAEQI	VIKITDQGYV	TSHGDHYHY	NGKVPYDAII	100
SEELLMKDP	N	YQLKSDIVN	EIKGGYVIKV	DGKYYVYLKD	AAHADNIRTK	150
EEIKRQKQEH		SHNHNSRADN	AVAAAAAQGR	YTTDDGYIFN	ASDIIEDTGD	200
AYIVPHGDHY		HYIPKNELSA	SELAAAEAYW	NGKQGSRPSS	SSSYNANPVQ	250
PRLSENHNLT		VTPTYHQNG	ENISSLLREL	YAKPLSERHV	ESDGLIFDPA	300
QITSRTARGV		AVPHGNHYHF	IPYEQMSELE	KRIARIIPLR	YRSNHWVPDS	350
RPEQPSPOST		PEPSPSLQPA	PNPQPAPSNP	IDEKLVKEAV	RKVG DG YVFE	400
ENGVSRYIPA		KDLSAETAAG	IDSKLAKQES	LSHKLGA KKT	DLPSSDREFY	450
NKAYDLLARI		HQDLLDNKGR	QVDFEVL DNL	LERLKDVS SD	KVKLVDDILA	500
FLAPIRHPER		LGKPNAQITY	TDDEIQVAKL	AGKYTTEDGY	IFDPRDITSD	550
EGDAYVT PHM		THSHWIKKDS	LSEAERAAAQ	AYAKEKGLTP	PSTDHQDSGN	600
TEAKGAEAIY		NRVKA AKVP	LDRMPYNLQY	TVEVKNGSLI	IPHYDHYHNI	650
KFEWFDEGLY		EAPKGYSLED	LLATVKYYVE	HPNERPHSDN	GFGNASDHVR	700
KNKADQDSKP		DEDKEHDEVS	EPHPESDEK	ENHAGLNPSA	DNLYKPSTDT	750
EETEEEAEDT		TDEAEIPQVE	NSVINAKIAD	AEALLEKVTD	PSIRQNAMET	800
LTGLKSSLLL		GTKDNNTISA	EVDSLLALLK	ESQPAPIQ		838

(SEQ ID NO : 14)

FIGURE 17

TGTGCTATG	CACTAAACCA	GCATCGTTCG	CAGGAAAATA	AGGACAATAA	TCGTGTCTCT	60
TATGTGGATG	GCAGCCAGTC	AAGTCAGAAA	AGTGAAAACT	TGACACCAGA	CCAGGTTAGC	120
CAGAAAGAAG	GAATTCAGGC	TGAGCAAATT	GTAATCAAAA	TTACAGATCA	GGGCTATGTA	180
ACGTACACAG	GTGATCACTA	TCATTACTAT	AATGGGAAAG	TTCTTTATGA	TGCCCTCTTT	240
AGTGAAGAAC	TCTTGATGAA	GGATCCAAAC	TATCAACTTA	AAGACGCTGA	TATTGTCAAT	300
GAAGTCAAGG	GTGGTTATAT	CATCAAGGTC	GATGGAAAAT	ATTATGTCTA	CCTGAAAGAT	360
GCAGCTCATG	CTGATAATGT	TCGAACTAAA	GATGAAATCA	ATCGTCAAAA	ACAAGAACAT	420
GTCAAAGATA	ATGAGAAGGT	TAACCTAAT	GTTGCTGTAG	CAAGGTCTCA	GGGACGATAT	480
ACGACAAATG	ATGGTTATGT	CTTTAATCCA	GCTGATATTA	TCGAAGATAC	GGGTAATGCT	540
TATATCGTTC	CTCATGGAGG	TCATATCAC	TACATTCCCA	AAAGCGATTT	ATCTGCTAGT	600
GAATTAGCAG	CAGCTAAAGC	ACATCTGGCT	GGAAAAAATA	TGCAACCGAG	TCAGTTAAGC	660
TATTCTTCAA	CACCTTCTCC	ATCTCTTCCA	ATCAATCCAG	GAACCTCACA	TGAGAAACAT	720
GAAGAAGATG	GATACGGATT	TGATGCTAAT	CGTATTATCG	CTGAAGATGA	ATCAGGTTTT	780
GTCATGAGTC	ACGGAGACCA	CAATCATTAT	TTCTTCAAGA	AGGACTTGAC	AGAAGAGCAA	840
ATTAAGGCTG	CGCAAAAACA	TTTAGAGGAA	GTTAAAACTA	GTCATAATGG	ATTAGATTCT	900
TTGTCTCTC	ATGAACAGGA	TTATCCAAGT	AATGCCAAAG	AAATGAAAGA	TTTAGATAAA	960
AAAATCGAAG	AAAAAATTGC	TGGCAATTATG	AAACAATATG	GTGTCAAACG	TGAAAGTATT	1020
GTCGTGAATA	AAGAAAAAAA	TGCGATTATT	TATCCGCATG	GAGATCACCA	TCATGCAGAT	1080
CCGATTGATG	AACATAAACC	GGTTGGAATT	GGTCATTCTC	ACAGTAACTA	TGAAGTGT	1140
AAACCCGAAG	AAGGAGTTGC	TAAAAAGAA	GGGAATAAAG	TTTATACTGG	AGAAGAATTA	1200
ACGAATGTTG	TTAATTTGTT	AAAAAATAGT	ACGTTTAATA	ATCAAACTT	TACTCTAGCC	1260
AATGGTCAAA	AACGCGTTTT	TTTTAGTTTT	CCGCTTGAAT	TGGAGAAAAA	ATTAGGTATC	1320
AATATGCTAG	TAAATTTAAT	AACACCAGAT	GGAAAAGTAT	TGGAGAAAGT	ATCTGGTAAA	1380
GTATTTGGAG	AAGGAGTAGG	GAATATTGCA	AACCTTGAAT	TAGATCAACC	TTATTTACCA	1440
GGACAAACAT	TTAAGTATAC	TATCGCTTCA	AAAGATTATC	CAGAAGTAAG	TTATGATGGT	1500
ACATTTACAG	TTCCAACCTC	TTTAGCTTAC	AAAATGGCCA	GTCAAACGAT	TTTCTATCCT	1560
TTCCATGCAG	GGGATACTTA	TTTAAGAGTG	AACCTCAAT	TTGCAGTGCC	TAAAGGAAC	1620
GATGCTTTAG	TCAGAGTGTT	TGATGAATTT	CATGGAAATG	CTTATTTAGA	AAATAACTAT	1680
AAAGTTGGTG	AAATCAAATT	ACCGATTCCG	AAATTAACC	AAGGAACAAC	CAGAACGGCC	1740
GGAAATAAAA	TTCTGTAAAC	CTTCATGGCA	AATGCTTATT	TGGACAATCA	ATCGACTTAT	1800
ATTGTGGAAG	TACCTATCTT	GGAAAAAGAA	AATCAAACTG	ATAAACCAAG	TATTCTACCA	1860
CAATTTAAAA	GGAATAAAGC	ACAAGAAAAAC	TCAAAACTTG	ATGAAAAGGT	AGAAGAACCA	1920
AAGACTAGTG	AGAAGGTAGA	AAAAGAAAAA	CTTTCTGAAA	CTGGGAATAG	TACTAGTAAT	1980
TCAACGTTAG	AAGAAGTTCC	TACAGTGGAT	CCTGTACAAG	AAAAAGTAGC	AAAATTTGCT	2040
GAAAGTTATG	GGATGAAGCT	AGAAAAATGTC	TTGTTTAATA	TGGACGGAAC	AATTGAATTA	2100
TATTTACCAT	CGGGAGAAGT	CATTAAAAAG	AATATGGCAG	ATTTTACAGG	AGAAGCACCT	2160
CAAGGAAATG	GTGAAAAATA	ACCATCTGAA	AATGGAAAAAG	TATCTACTGG	AACAGTTGAG	2220
AACCAACCAA	CAGAAAAATA	ACCAGCAGAT	TCTTTACCAG	AGGCACCAAA	CGAAAAACCT	2280
GTAACCAACAG	AAAATCAAC	GGATAATGGA	ATGTTGAATC	CAGAAGGGAA	TGTGGGGAGT	2340
GACCCATATG	TAGATTCAGC	ATTAGAGGAA	GCTCCAGCAG	TAGATCCTGT	ACAAGAAAAA	2400
TTAGAAAAAT	TTACAGCTAG	TTACGGATTA	GGCTTAGATA	GTGTTATATT	CAATATGGAT	2460
GGAACGATTG	AATTAAGATT	GCCAAGTGGG	GAAGTGATAA	AAAAGAAATT	ATTGATCTCA	2520
TAGCGTAA	(SEQ ID NO : 15)					2528

FIGURE 18

CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	SENLTDPQVS	OKEGIAEQI	50
VIKITDQGYV	TSHGDHYHY	NGKVPYDALF	SEELLMKDPN	YQLKDADIVN	100
EVKGGYIIKV	DGKYVYVKD	AAHADNVRTK	DEINRQKQEH	VKDNEKVNSN	150
VAVARSQGRY	TTNDGYVFNP	ADIIEDTGNA	YIVPHGGHYH	YIPKSDLSAS	200
ELAAAKAHLA	GKNMQPSQLS	YSSTPSPSLP	INPGTSHEKH	EEDGYGFDAN	250
RIIAEDES GF	VMSHGDHNY	FFKKDLTEEQ	IKAAQKHLEE	VKTSHNGLDS	300
LSSHEQDYP	NAKEMKDLK	KIEEKIAGIM	KQYGVKRESI	VVNKEKNAIL	350
YPHGDHHD	PIDEHKPVG	GHSNHYELF	KPEEGVAKKE	GKNVYTGEEL	400
TNVNLLKNS	TFNNQNF	NGQKRVSF	PPELEKKLGI	NMLVKLITPD	450
GKVLKVS	VFGGVGNIA	NFELDQPYLP	GQTFKYTIAS	KDYPEVSYDG	500
TFTVPTSLAY	KMASQTIFY	FHAGDYLTV	NPQFAVPKGT	DALVRVDEF	550
HGNAYLENNY	KVGEIKLPI	KLNQGTTRTA	GNKIPVTFMA	NAYLDNQSTY	600
IVEVPILEKE	NQTDKPSILP	QFKRNKAQEN	SKLDEKVEEP	KTSEKVEKEK	650
LSETGNSTSN	STLEEVP	PVQEKVAKFA	ESYGMKLENV	LFNMDGTIEL	700
YLPSEGEVIK	NMADFTGEAP	QNGENKPS	NGKVSTGTVE	NQPTENKPAD	750
SLPEAPNEKP	VKPNSTDN	MLNPEGNVGS	DPMLDSALEE	APAVDPVQEK	800
LEKFTASYGL	GLDSVIFNMD	GTIELRLPSG	EVIKNLLIS		840

(SEQ ID NO : 16)

FIGURE 19

CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	SENLTDPQVS	OKEGIAEQI	50
VIKITDQGYV	TSHGDHYHY	NGKVPYDALF	SEELLMKDPN	YQLKDADIVN	100
EVKGGYIIKV	DGKYVYVKD	AAHADNVRTK	DEINRQKQEH	VKDNEKVNSN	150
VAVARSQGRY	TTNDGYVFNP	ADIIEDTGNA	YIVPHGGHYH	YIPKSDLSAS	200
ELAAAKAHLA	GKNMQPSQLS	YSSTASDNMT	QSVAKGSTSK	PANKSENLOS	250
LLKELYDSPS	AQRYSESDGL	VFDPAKIISR	TPNGVAIPHG	DHYHFIPYSK	300
LSALEEKIAR	MVPISGTGST	VSTNAKPNEV	VSSLGSLSSN	PSSLTTSKEL	350
SSASDGYIFN	PKDIVEETAT	AYIVRHGDHF	HYIPKSNQIG	QPTLPNNSLA	400
TPSPSLPINP	GTSHEKHEED	GYGFDANRII	AEDESGFVMS	HGDHNYFFK	450
KDLTEEQIKA	AQKHLEEVKT	SHNGLDSLSS	HEQDYPGNAK	EMKDLKKIE	500
EKIAGIMKQY	GVKRESIVVN	KEKNAIYPH	GDHHHADPID	EHPVGIGHS	550
HSNYELFKPE	EGVAKKEGK	VYTGEELTNV	VNLLKNSTFN	NQNFTLANGQ	600
KRVSFSPPE	LEKKLGINML	VKLITPDGKV	LEKVSQKVF	EGVGNIANFE	650
LDQPYLPQGT	FKYTIASKDY	PEVSYDGTFT	VPTSLAYKMA	SQTIFYPFHA	700
GDYLRVNPQ	FAVPKGTDAL	VRVDEFHGN	AYLENNYKVG	EIKLPIPKLN	750
QGTTRTAGNK	IPVTFMANAY	LDNQSTYIVE	VPILEKENQT	DKPSILPQFK	800
RNKAQENSKL	DEKVEEPKTS	EKVEKEKLSE	TGNSTSNSTL	EEVPTVDPVQ	850
EKVAKFAESY	GMKLENVLFN	MDGTIELYLP	SSEVIKKNMA	DFTGEAPQGN	900
GENKPSENGK	VSTGTVENQP	TENKPADSLP	EAPNEKPVKP	ENSTDNGLN	950
PEGNVGSDPM	LDPALEEAPA	VDPVQEKLEK	FTASYGLGLD	SVIFNMDGTI	1000
ELRLPSGEVI	KQNLSDFIA				1019

(SEQ ID NO : 55)

FIGURE 20

CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	SENLTDPQVS	QKEGIAEQI	50
VIKITDQGYV	TSHGDHYHY	NGKVPYDALF	SEELLMKDPN	YQLKDADIVN	100
EVKGGYIIKV	DGKYVYVLKD	AAHADNVRTK	DEINRQKQEH	VKDNEKVNSN	150
VAVARSQGRY	TTNDGYVFNP	ADIIEDTGNA	YIVPHGGHYH	YIPKSDLSAS	200
ELAAAKAHLA	GKNMQPSQLS	YSSTASDNNT	QSVAKGSTSK	PANKSENLOS	250
LLKELYDSPS	AQRYSEDGDL	VFDPAKIISR	TPNGVAIPHG	DHYHFIPYSK	300
LSALEEKIAR	MVPISGTGST	VSTNAKPNEV	VSSLGSLSSN	PSSLTTSKEL	350
SSASDGYIFN	PKDIVEETAT	AYIVRHGDHF	HYIPKSNQIG	QPTLPNNSLA	400
TPSPSLPINP	GTSHEKHEED	GYGFDANRII	AEDESGFVMS	HGDHNNHYFFK	450
KDLTEEQIKA	AQKHLEEVKT	SHNGLDSLSS	HEQDYPGNA		489

(SEQ ID NO : 56)

FIGURE 21

MKFSKKYIAA	GSIVIVLSL	CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	SENLTDPQVS	60
QKEGIAEQI	VIKITDQGYV	TSHGDHYHY	NGKVPYDALF	SEELLMKDPN	YQLKDADIVN	120
EVKGGYIIKV	DGKYVYVLKD	AAHADNVRTK	DEINRQKQEH	VKDNEKVNSN	VAVARSQGRY	180
TTNDGYVFNP	ADIIEDTGNA	YIVPHGGHYH	YIPKSDLSAS	ELAAAKAHLA	GKNMQPSQLS	240
YSSTASDNNT	QSVAKGSTSK	PANKSENLOS	LLKELYDSPS	AQRYSEDGDL	VFDPAKIISR	300
TPNGVAIPHG	DHYHFIPYSK	LSALEEKIAR	MVPISGTGST	VSTNAKPNEV	VSSLGSLSSN	360
PSSLTTSKEL	SSASDGYIFN	PKDIVEETAT	AYIVRHGDHF	HYIPKSNQIG	QPTLPNNSLA	420
TPSPSLPINP	GTSHEKHEED	GYGFDANRII	AEDESGFVMS	HGDHNNHYFFK	KDLTEEQIKA	480
AQKHLEEVKT	SHNGLDSLSS	HEQDYPGNA				509

(SEQ ID NO : 57)

FIGURE 22

DLTEEQIKAA	QKHLEEVKTS	HNGLDSLSSH	EQDYPGNAKE	MKDLDKKIEE	50
KIAGIMKQYG	VKRESIVVVK	EKNAIIPHG	DHHHADPIDE	HKPVGIGHSH	100
SNYELFKPEE	GVAKKEGNKV	YTGEELTNVV	NLLKNSTFNN	QNFTLANGQK	150
RVSFSFPPEL	EKKLGINMLV	KLITPDGKVL	EKVSQKVFGE	GVGNIANFEL	200
DQPYLPGQTF	KYTIASKDYP	EVSYDGTFTV	PTSLAYKMAS	QTIFYPFHAG	250
DTYLRVNPQF	AVPKGTDALV	RVFDEFHGNA	YLENNYKVGE	IKLPIPKLNQ	300
GTRTAGNKI	PVTFMANAYL	DNQSTYIVEV	PILEKENQTD	KPSILPOFKR	350
NKAQENSKLD	EKVEEPTSE	KVEKEKLSET	GNSTSNSTLE	EVPTVDPVQE	400
KVAKFAESYG	MKLENVLFNM	DGTIELYLPS	GEVIKKNMAD	FTGEAPQNG	450
ENKPSSENGKV	STGTVENOPT	ENKPADSLPE	APNEKPVKPE	NSTDNGMLNP	500
EGNVGSDPML	DPALEEAPAV	DPVQEKLEKF	TASYGLGLDS	VIFNMDGTIE	550
LRLPSGEVIK	KNLSDFIAKL	RYRSNHWVPD	SRPEEPSQPQ	TPEPSPSQPQ	600
APNPQPAPSN	PIDEKLVKEA	VRKVG DG YVF	EENGVSRYIP	AKNLSAETAA	650
GIDSKLAKQE	SLSHKLGAKK	TDLPSDDREF	YNKAYDLLAR	IHQDLLDNKG	700
RQVDFEALDN	LLERLKDVSS	DKVKLVDDIL	AFLAPIRHPE	RLGKPNQAQT	750
YTDDEIQVAK	LAGKYTTEDG	YIFDPRDITS	DEGDAYVTPH	MTHSHWIKKD	800
SLSEAERAAA	QAYAKEKGLT	PPSTDHQDSG	NTEAKGAEAI	YNRVKAACKV	850
PLDRMPYNLQ	YTVFVKNKSL	IIPHYDHYHN	IKFEWFDEGL	YEAPKGYTLE	900
DLLATVKYIV	EHPNERPHSD	NGFGNASDHV	QRNKGQADT	NQTEKPSEEK	950
PQTEKPEEET	PREEKPQSEK	PESPKPTEEP	EEESPSESEE	PQVETEKVEE	1000
KLREAEDLLG	KIQDPPIKSN	AKETLTGLKN	NLLFGTQDNN	TIMAEAEKLL	1050
ALLKESK					1057

(SEQ ID NO : 58)

FIGURE 23

CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	SENLTPOQVS	QKEGIAEQI	50
VIKITDQGYV	TSHGDHYHYY	NGKVPYDALF	SEELLMKDPN	YQLKDADIVN	100
EVKGGYIIKV	DGKYVYVLKD	AAHADNVRTK	DEINRQKQEH	VKDNEKVNSN	150
VAVARSQGRY	TTNDGYVFNP	ADIIEDTGNA	YIVPHGGHYH	YIPKSDLSAS	200
ELAAA	(SEQ ID NO : 59)				205

FIGURE 24

CAYELGLHQA	QTVKENNRVS	YIDGKQATQK	TENLTPDEV	KREGINAEQI	50
VIKITDQGYV	TSHGDHYHYY	NGKVPYDAII	SEELLMKDPN	YQLKDSDIVN	100
EIKGGYVIKV	NGKYVYVLKD	AAHADNVRTK	EEINRQKQEH	SQHREGGTS	150
NDGAVAFARS	QGRYTTDDGY	IFNASDIIED	TGDAYIVPHG	DHYHYIPKNE	200
LSASELAAAE	AFLSGRENLS	NLRTYRRQNS	DNTPRTNWVP	SVSNPGTTNT	250
NTSNNSNTNS	QASQSNDDIDS	LLKQLYKLPL	SQRHVESDGL	IFDPAQITSR	300
TARGVAVPHG	NHYHFIPYEQ	MSELEKRIAR	IIPLYRSNH	WVPDSRPEEP	350
SPQPTPEPSP	SPQPAPNPQP	APSNPIDEKL	VKEAVRKVGD	GYVFEENGVS	400
RYIPAKNLSA	ETAAGIDSKL	AKQESLSHKL	GAKKTDLPSS	DREFYNKAYD	450
LLARIHQDLL	DNKGRQVDFE	ALDNLLERLK	DVSSDKVKLV	DDILAFLAPI	500
RHPERLGKPN	AQITYTDDDEI	QVAKLAGKYT	TEDGYIFDPR	DITSDEGDAY	550
VTPHMTSHHW	IKKDSLSEAE	RAAAQAYAKE	KGLTPPSTDH	QDSGNTAKG	600
AEAIYNRVKA	AKKVPLDRMP	YNLQYTVEVK	NGSLIIPHYD	HYHNIKFEWF	650
DEGLYEAPKG	YLEDLLATV	KYYVEHPNER	PHSDNGFGNA	SDHVQRNKNG	700
QADTNQTEKP	SEEKPTTEKP	EEETPREEKP	QSEKPESPKP	TEEPPEESPE	750
ESEEPQVETE	KVEEKLREAE	DLGKIQDPI	IKSNAKETLT	GLKNNLLFGT	800
QDNNTIMAEA	EKLALLKES	K	((SEQ ID NO : 60)		821

FIGURE 25

CAYELGLHQA	QTVKENNRVS	YIDGKQATQK	TENLTPDEV	KREGINAEQI	50
VIKITDQGYV	TSHGDHYHYY	NGKVPYDAII	SEELLMKDPN	YQLKDSDIVN	100
EIKGGYVIKV	NGKYVYVLKD	AAHADNVRTK	EEINRQKQEH	SQHREGGTS	150
NDGAVAFARS	QGRYTTDDGY	IFNASDIIED	TGDAYIVPHG	DHYHYIPKNE	200
LSASELAAAE	AFLSGRENLS	NLRTYRRQNS	DNTPRTNWVP	SVSNPGTTNT	250
NTSNNSNTNS	QASQSNDDIDS	LLKQLYKLPL	SQRHVESDGL	IFDPAQITSR	300
TARGVAVPHG	NHYHFIPYEQ	MSELEKRIAR	IIPL		334
(SEQ ID NO : 61)					

FIGURE 26

RYRSNHWVPD	SRPEEPSPOP	TPEPSPOP	APNPQAPSN	PIDEKLVKEA	50
VRKVGDDGYV	EENGVSRYIP	AKNLSAETAA	GIDSKLAKQE	SLSHKLGAKK	100
TDLPSDDREF	YNKAYDLLAR	IHQDLLDNKG	RQVDFEALDN	LLERLKDVS	150
DKVKLVDDIL	AFLAPIRHPE	RLGKPNQAIT	YTDDEIQVAK	LAGKYTTEDG	200
YIFDPRDITS	DEGDAYVTPH	MTHSHWIKKD	SLSEAERAAA	QAYAKEKGLT	250
PPSTDHQDSG	NTEAKGAEAI	YNRVKAAKKV	PLDRMPYNLO	YTVEVKNGSL	300
IIPHVDHYHN	IKFEWFDEGL	YEAPKGYTLE	DLLATVKYV	EHPNERPHSD	350
NGFGNASDHV	QRNKNGQADT	NQTEKPSEEK	PQTEKPEEET	PREEKPQSEK	400
PESPKPTEEP	EEESPEESEE	PQVETEKVEE	KLREAEDLLG	KIQDPIIKSN	450
AKETLTGLKN	LLFGTQDNM	TIMAEAEKLL	ALLKESK		487
(SEQ ID NO : 62)					

FIGURE 27

AEAFLSGREN	LSNLRITYRRQ	NSDNTPRTNW	VPSVSNPGTT	NTNTSNNST	50
NSQASQSDI	DSLLKQLYKL	PLSQRHVESD	GLIFDPAQIT	SRTARGVAVP	100
HGNHYHFIPY	EQMSELEKRI	ARIIPLYRYS	NHWVPDSRPE	EPSPQPTPEP	150
SPSPQPAPNP	QPAPSNPIDE	KLVKEAVRKV	GDGYVFEENG	VSRYIPAKNL	200
SAETAAGIDS	KLAKQESLSH	KLGAKKTDLP	SSDREFYNKA	YDLLARIHQD	250
LLDNKGRQVD	FEALDNLLER	LKDVSSDKVK	LVDDILAFIA	PIRHPERLGK	300
PNAQITYTDD	EIQVAKLAGK	YTTEDGYIFD	PRDITSDEGD	AYVTPHMTSH	350
HWIKQDSLSE	AERAAAQAYA	KEKGLTPPST	DHQDSGNTA	KGAEAIYNRV	400
KAACKVPLDR	MPYNLQYTV	VKNGSLIIPH	YDHYHNIKFE	WFDEGLYEAP	450
KGYTLEDLLA	TVKYYVEHPN	ERPHSDNGFG	NASDHVQRNK	NGQADTNQTE	500
KPSEKPKQTE	KPEEETPREE	KPQSEKPESP	KPTEEPPEES	PEESEEPQVE	550
TEKVEEKLRE	AEDLLGKIQD	PIIKSNAKET	LTGLKNLLF	GTQDNNTIMA	600
EAEKLLALLK	ESK	(SEQ ID NO : 63)			613

FIGURE 28

DLTEEQIKAA	QKHLEEVKTS	HNGLDLSSSH	EQDYPGNAKE	MKDLDKKIEE	50
KIAGIMKQYG	VKRESIVVNK	EKNAIIPYHG	DHHHADPIDE	HKPVGIGHSH	100
SNYELFKPEE	GVAKKEGNKV	YTGEELTNV	NLLKNSTFNN	QNFTLANGQK	150
RVSFSFPPEL	EKKLGINMLV	KLITPDGKVL	EKVSGKVFG	GVGNIANFEL	200
DQPYLPGQTF	KYTIASKDYP	EVSYDGTFTV	PTSLAYKMAS	QTIFYPPFHAG	250
DTYLRVNPQF	AVPKGTDALV	RVFDEFHGNA	YLENNYKVGE	IKLPIPKLNQ	300
GTTRTAGNKI	PVTFMANAYL	DNQSTYIVE	PILEKENQTD	KPSILPQFKR	350
NKAQENSKLD	EKVEEPTSE	KVEKEKLSET	GNSTSNSTLE	EVPTVDPVQE	400
KVAKFAESYG	MKLENVLFNM	DGTIELYLPS	GEVIKKNMAD	FTGEAPQNG	450
ENKPSSENGKV	STGTVENQPT	ENKPADSLPE	APNEKPVKPE	NSTDNGMLNP	500
EGNVGSDPML	DPALEEAPAV	DPVQEKLEKF	TASYGLGLDS	VIFNMDGTIE	550
LRLPSGEVIK	KNLSDFIA	(SEQ ID NO : 64)			568

FIGURE 29

DLTEEQIKAA	QKHLEEVKTS	HNGLDLSSSH	EQDYPGNAKE	MKDLDKKIEE	50
KIAGIMKQYG	VKRESIVVNK	EKNAIIPYHG	DHHHADPIDE	HKPVGIGHSH	100
SNYELFKPEE	GVAKKEGNKV	YTGEELTNV	NLLKNSTFNN	QNFTLANGQK	150
RVSFSFPPEL	EKKLGINMLV	KLITPDGKVL	EKVSGKVFG	GVGNIANFEL	200
DQPYLPGQTF	KYTIASKDYP	EVSYDGTFTV	PTSLAYKMAS	QTIFYPPFHAG	250
DTYLRVNPQF	AVPKGTDALV	RVFDEFHGNA	YLENNYKVGE	IKLPIPKLNQ	300
GTTRTAGNKI	PVTFMANAYL	DNQSTYIVE	(SEQ ID NO : 65)		329

FIGURE 30

EVPILEKENQ	TDKPSILPOF	KRNKAQENSK	LDEKVEEPT	SEKVEKEKLS	50
ETGNSTSNST	LEEVPTVDPV	QEKVAKFAES	YGMKLENVLF	NMDGTIELYL	100
PSGEVIKKNM	ADFTGEAPOG	NGENKPSENG	KVSTGTVENQ	PTENKPADSL	150
PEAPNEKPVK	PENSTDNGML	NPEGNVGSDP	MLDPALEEAP	AVDPVQEKLE	200
KFTASYGLGL	DSVIFNMDGT	IELRLPSGEV	IKKNLSDFIA		240

(SEQ ID NO : 66)

FIGURE 31

DIDSLLKQLY	KLPLSQRHVE	SDGLIFDPAQ	ITSRTARGVA	VPHGNHYHFI	50
PYEQMSELEK	RIARIIPRLY	RSNHVVPDSR	PEEPSPOPTP	EPSPSQPAP	100
NPQPAPSNPI	DEKLVKEAVR	KVG DGYVFEE	NGVSRYIPAK	NLSAETAAGI	150
DSKLAKQESL	SHKLGAKKTD	LPSSDREFYN	KAYDLLARIH	QDLLDNKGRQ	200
VDFEALDNLL	ERLKDVSDDK	VKLVDLILAF	LAPIRHPERL	GKPNAQITYT	250
DDEIQVAKLA	GKYTTEDGYI	FDPRDITSDE	GDAYVTPHMT	HSHWIKKDSL	300
SEAERAAAQA	YAKEKGLTPP	STDHQDSGNT	EAKGAEAIYN	RVKAAKKVPL	350
DRMPYNLQYT	VEVKNGSLII	PHYDHYHNIK	FEWFDEGLYE	APKGYTTLEDL	400
LATVKYYVEH	PNERPHSDNG	FGNASDHVQR	NKNGQADTNQ	TEKPSEEKPO	450
TEKPEEETPR	EKPQSEKPE	SPKPTEEPPE	ESPEESEEPQ	VETEKVEEKL	500
REAEDLLGKI	QDPIKSNK	ETLTGLKNNL	LFGTQDNNTI	MAEAELLLAL	550
LKESK	(SEQ ID NO : 67)				555

FIGURE 32

DIDSLLKQLY	KLPLSQRHVE	SDGLIFDPAQ	ITSRTARGVA	VPHGNHYHFI	50
PYEQMSELEK	RIARIIPRLY	RSNHVVPDSR	PEEPSPOPTP	EPSPSQPAP	100
NPQPAPSNPI	DEKLVKEAVR	KVG DGYVFEE	NGVSRYIPAK	NLSAETAAGI	150
DSKLAKQESL	SHKLGAKKTD	LPSSDREFYN	KAYDLLARIH	QDLLDNKGRQ	200
VDFEALDNLL	ERLKDVSDDK	VKLVDLILAF	LAPIRHPERL	GKPNAQITYT	250
DDEIQVAKLA	GKYTTEDGYI	FDPRDITSDE	GDAYVTPHMT	HSHWIKKDSL	300
SEAERAAAQA	YAKEKGLTPP	STDHQDSGNT	EAKGAEAIYN	RVKAAKKVPL	350
DRMPYNLQYT	VEVKNGSLII	PHYDHYHNIK	FEWFDEGLYE	APKGYTTLEDL	400
LATVKYYVEH	PNERPHSDNG	FGNASDHV	(SEQ ID NO : 68)		428

FIGURE 33

GLYEAPKGYT	LEDLLATVKY	YVEHPNERPH	SDNGFGNASD	HVQRNKGQA	50
DTNQTEKPSE	EKPQTEKPEE	ETPREKPKQS	EKPESPKPTE	EPEEESPEES	100
EEPQVETEKV	EEKLREAEDL	L	(SEQ ID NO : 69)		121

FIGURE 34

ASDHVQRNKN	GQADTNQTEK	PSEKPKQTEK	PEEETPREK	PQSEKPESPK	50
PTEPEEESP	ESEEPQVET	EKVEEKLREA	EDLLGKIQDP	IIKSNKATL	100
TGLKNNLLFG	TQDNNTIMAE	AEKLLALLKE	SK		132

(SEQ ID NO : 70)

FIGURE 35

DIDSLKQLY KLPLSQRHVE SDGLIFDPAQ ITSRTARGVA VPHGNHYHFI	50
PYEQMSELEK RIARIIPRY RSNHWVPDSR PEEPSQPTP EPSPSQPAP	100
NPQPAPSNPI DEKLVKEAVR KVG DGYVFEE NGVSRYIPAK NLSAETAAGI	150
DSKLAKQESL SHKLGAKKTD LPSSDREFYN KAYDLLARIH QDLLDNKGRQ	200
VDFEALDNLL ERLKDVSSDK VKLVDD (SEQ ID NO : 71)	226

FIGURE 36

DILAFLAPIR HPERLGKPNQ QITYTDEIQ VAKLAGKYTT EDGYIFDPRD	50
ITSDEGDAYV TPHMTHSHWI KKDSLSEAEER AAAQAYAKEK GLTPPSTDHQ	100
DSGNTAEKGA EAIYNRVKAA KKVPLDRMPY NLQYTTVEVKN GSLIIPHYDH	150
YHNIKFEWFD EGLYEAPKGY TLEDLLATVK YYVEHPNERP HSDNGFGNAS	200
DHV (SEQ ID NO : 72)	203

FIGURE 37

CSYELGRHQA GQVKKESNRV SYIDGQAGQ KAENLTPDEV SKREGINAEQ	50
IVIKITDQGY VTSHGDHYHY YNGKVPYDAI ISEELMKDP NYQLKDS DIV	100
NEIKGGYVIK VDGKYYVYLK DAAHADNIRT KEEIKRQKQE HSHNHNSRAD	150
NAVAAAAAQG RYTDDGYIF NASDIEDTG DAYIVPHGDH YHYIPKNELS	200
ASELAAAEAY WNGKQGSRPS SSSSYNANPV QPRLSENHNL TVTPTYHQNQ	250
GENISSLLRE LYAKPLSERH VESDGLIFDP AQITSRTARG VAVPHGNHYH	300
FIPYEQMSEL EKRIARIIPR RYRSNHWVPD SRPEQSPQS TPEPSPSLQP	350
APNPQPAPSN PIDEKLVKEA VRKVG DGYVF EENGVSRYIP AKDLSAETAA	400
GIDSKLAKQE SLSHKLGAKK TDLPSDREF YNKAYDLLAR IQDLLDNKG	450
RQVDFEVLN LERLKDVS DKVKLVDDIL AFLAPIRHPE RLKGPNAQIT	500
YTDEIQVAK LAGKYTTEDG YIFDPRDITS DEGDAYVTPH MTHSHWIKD	550
SLSEAEAAA QAYAKEKGLT PPSTDHQDSG NTEAKGAEAI YNRVKAACKV	600
PLDRMPYNLQ YTVEVKNGSL IIPHYDHYHN IKFEWFDEGL YEAPKGYSLE	650
DLATVKYYV EHPNERPHSD NGFGNASDHV RKNKADQDSK PDEDKEHDEV	700
SEPTHPESDE KENHAGLNPS ADNLYKPSTD TEETEEEAED TTDEAEIPQV	750
ENSVINAKIA DAEALLEKVT DPSIRQNAME TLTGLKSSLL LGTKDNNTIS	800
AEVDSLLALL KESQPAPIQ (SEQ ID NO : 73)	819

FIGURE 38

ENISSLLREL YAKPLSERHV ESDGLIFDPA QITSRTARGV AVPHGNHYHF	50
IPYEQMSELE KRIARIIPR YRSNHWVPDS RPEQSPQST PEPSPSLQPA	100
PNPQPAPSNP IDEKLVKEAV RKVG DGYVFE ENGVSRYIPA KDLSAETAAG	150
IDSKLAKQES LSHKLGAKKT DLPSSDREFY NKAYDLLARI HQDLLDNKGR	200
QVDFEVLN LERLKDVS DKVKLVDDILA FLAPIRHPE LGKPNQITY	250
TDDEIQVAKL AGKYTTEDGY IFDPRDITS EGDAYVTPH MTHSHWIKD	300
LSEAEAAAQ AYAKEKGLTP PSTDHQDSGN TEAKGAEAI YNRVKAACKV	350
LDRMPYNLQY TVEVKNGSLI IIPHYDHYHN KFEWFDEGLY EAPKGYSLE	400
LLATVKYYVE HPNERPHSDN GFGNASDHV RKNKADQDSK PDEDKEHDEV	450
EPHPSDEK ENHAGLNPS ADNLYKPSTD TEETEEEAED TTDEAEIPQV	

VRKNKADQDS KPDEDKEHDE VSEPTHPESD EKENHAGLNP SADNLYKPST 50
 DTEETEEEEE DTTDEAEIPQ VENSVINAKI ADAEALLEKV TDPSIRQNAM 100
 ETLTGLKSSL LLGTKDNNTI SAEVDSLALL LKESQPAPIQ 140
 (SEQ ID NO : 75)

FIGURE 40

GACTTGACAG	AAGAGCAAAT	TAAGGCTGCG	CAAAAACATT	TAGAGGAAGT	50
TAAAACTAGT	CATAATGGAT	TAGATTCTTT	GTCTATCTCAT	GAACAGGATT	100
ATCCAGGTAA	TGCCAAAGAA	ATGAAAGATT	TAGATAAAAA	AATCGAAGAA	150
AAAATTGCTG	GCATTATGAA	ACAATATGGT	GTCAAACGTG	AAAGTATTGT	200
CGTGAATAAA	GAAAAAATG	CGATTATTTA	TCCGCATGGA	GATCACCATC	250
ATGCAGATCC	GATTGATGAA	CATAAACCGG	TTGGAATTGG	TCATTCTCAC	300
AGTAACTATG	AACTGTTTAA	ACCCGAAGAA	GGAGTTGCTA	AAAAAGAAGG	350
GAATAAAGTT	TATACTGGAG	AAGAATTAAC	GAATGTTGTT	AATTGTGTTA	400
AAAATAGTAC	GTTTAATAAT	CAAAACTTTA	CTCTAGCCAA	TGGTCAAAAA	450
CGCGTTTCTT	TTAGTTTTC	GCCTGAATTG	GAGAAAAAAT	TAGGTATCAA	500
TATGCTAGTA	AAATTAATAA	CACCAGATGG	AAAAGTATTG	GAGAAAGTAT	550
CTGGTAAAGT	ATTTGGAGAA	GGAGTAGGGA	ATATTGCAAA	CTTTGAATTA	600
GATCAACCTT	ATTTACCAGG	ACAAACATTT	AAGTATACTA	TCGCTTCAAA	650
AGATTATCCA	GAAGTAAGTT	ATGATGGTAC	ATTTACAGTT	CCAACCTCTT	700
TAGCTTACAA	AATGGCCAGT	CAAACGATTT	TCTATCCTTT	CCATGCAGGG	750
GATACTTATT	TAAGAGTGAA	CCCTCAATTT	GCAGTGCCCTA	AAGGAACTGA	800
TGCTTTAGTC	AGAGTGTTTG	ATGAATTTCA	TGGAAATGCT	TATTTAGAAA	850
ATAACTATAA	AGTTGGTGAA	ATCAAATTAC	CGATTCCGAA	ATTAAACCAA	900
GGAACAACCA	GAACGGCCGG	AAATAAAATT	CCTGTAACCT	TCATGGCAAA	950
TGCTTATTTG	GACAACTCAAT	CGACTTATAT	TGTGGAAGTA	CCTATCTTGG	1000
AAAAAGAAAA	TCAAATGAT	AAACCAAGTA	TTCTACCACA	ATTTAAAGG	1050
AATAAGCAC	AAGAAAACCT	AAAACCTGAT	GAAAAGGTAG	AAGAACCATA	1100
GACTAGTGAG	AAGGTAGAAA	AAGAAAAACT	TTCTGAAACT	GGAATAGTA	1150
CTAGTAATTC	AACGTTAGAA	GAGTTTCCTA	CAGTGGATCC	TGTACAAGAA	1200
AAAGTAGCAA	AATTTGCTGA	AAGTTATGGG	ATGAAGCTAG	AAAATGTCTT	1250
GTTTAAATATG	GACGGAACAA	TTGAATTATA	TTTACCATCA	GGAGAAGTCA	1300
TTAAAAAGAA	TATGGCAGAT	TTTACAGGAG	AAGCACCTCA	AGGAAATGGT	1350
GAAAATAAAC	CATCTGAAAA	TGGAAGAGTA	TCTACTGGAA	CAGTTGAGAA	1400
CCAACCAACA	GAAAATAAAC	CAGCAGATTC	TTTACCAGAG	GCACCAACG	1450
AAAAACCTGT	AAAACCAGAA	AACTCAACGG	ATAATGGAAT	GTTGAATCCA	1500
GAAGGGAATG	TGGGGAGTGA	CCCTATGTTA	GATCCAGCAT	TAGAGGAAGC	1550
TCCAGCAGTA	GATCCTGTAC	AAGAAAAATT	AGAAAAAATT	ACAGCTAGTT	1600
ACGGATTAGG	CTTAGATAGT	GTTATATTCA	ATATGGATGG	AACGATTGAA	1650
TTAAGATTGC	CAAGTGGAGA	AGTGATAAAA	AAGAATTTAT	CTGATTTTAT	1700
AGCGAAGCTT	CGTTATCGTT	CAAACCATTT	GGTACCAGAT	TCAAGACCAG	1750
AAGAACCAAG	TCCACAACCG	ACTCCAGAAC	CTAGTCCAAG	TCCGCAACCT	1800
GCACCAAAATC	CTCAACACG	TCCAAGCAAT	CCAATTGATG	AGAAATTGGT	1850
CAAAGAAGCT	GTTGGAAGAG	TAGGCGATGG	TTATGTCTTT	GAGGAGAATG	1900
GAGTTTCTCG	TTATATCCCA	GCCAAGAAATC	TTTCAGCAGA	AACAGCAGCA	1950
GGCATTGATA	GCAAACTGGC	CAAGCAGGAA	AGTTTATCTC	ATAAGCTAGG	2000
AGCTAAGAAA	ACTGACCTCC	CATCTAGTGA	TCGAGAATTT	TACAATAAGG	2050
CTTATGAÇTT	ACTAGCAAGA	ATTCACCAAG	ATTTACTTGA	TAATAAAGGT	2100
CGACAAGTTG	ATTTTGAGGC	TTTGGATAAC	CTGTTGGAAC	GACTCAAGGA	2150
TGTCTCAAGT	GATAAAGTCA	AGTTAGTGGA	TGATATTCTT	GCCTTCTTAG	2200
CTCCGATTCTG	TCATCCAGAA	CGTTTAGGAA	AACCAAATGC	GCAAATTACC	2250
TACACTGATG	ATGAGATTCA	AGTAGCCAAG	TTGGCAGGCA	AGTACACAAC	2300
AGAAGACGGT	TATATCTTTG	ATCCTCGTGA	TATAACCAGT	GATGAGGGGG	2350
ATGCCTATGT	AACTCCACAT	ATGACCCATA	GCCACTGGAT	TAAAAAAGAT	2400

AGTTTGTCTG	AAGCTGAGAG	AGCGGCAGCC	CAGGCTTATG	CTAAAGAGAA	2450
AGGTTTGACC	CCTCCTTCGA	CAGACCATCA	GGATTCAGGA	AATACTGAGG	2500
CAAAAGGAGC	AGAAGCTATC	TACAACCGCG	TGAAAGCAGC	TAAGAAGGTG	2550
CCACTTGATC	GTATGCCTTA	CAATCTTCAA	TATACTGTAG	AAGTCAAAAA	2600
CGGTAGTTTA	ATCATACCTC	ATTATGACCA	TTACCATAAC	ATCAAATTTG	2650
AGTGGTTTGA	CGAAGGCCTT	TATGAGGCAC	CTAAGGGGTA	TACTCTTGAG	2700
GATCTTTTGG	CGACTGTCAA	GTACTATGTC	GAACATCCAA	ACGAACGTCC	2750
GCATTGAGAT	AATGGTTTTG	GTAACGCTAG	CGACCATGTT	CAAAGAAACA	2800
AAAATGGTCA	AGCTGATACC	AATCAAACGG	AAAAACCAAG	CGAGGAGAAA	2850
CCTCAGACAG	AAAAACCTGA	GGAAGAAACC	CCTCGAGAAG	AGAAACCACA	2900
AAGCGAGAAA	CCAGAGTCTC	CAAAACCAAC	AGAGGAACCA	GAAGAAGAAT	2950
CACCAGAGGA	ATCAGAAGAA	CCTCAGGTCG	AGACTGAAAA	GGTTGAAGAA	3000
AAACTGAGAG	AGGCTGAAGA	TTTACTTGGA	AAAATCCAGG	ATCCAATTAT	3050
CAAGTCCAAT	GCCAAAGAGA	CTCTCACAGG	ATTAAAAAAT	AATTACTAT	3100
TTGGCACCCA	GGACAACAAT	ACTATTATGG	CAGAAGCTGA	AAAACATTG	3150
GCTTTATTAA	AGGAGAGTAA	G	(SEQ ID NO : 76)		3171

FIGURE 41

EAYWNGKQGS	RPSSSSSYNA	NPVQPRLESEN	HNLTVTPTYH	QNQGENISL	50
LRELYAKPLS	ERHVESDGLI	FDPAQITSRT	ARGVAVPHGN	HYHFIPYEQM	100
SELEKRIARI	IPLRYRSNHV	VPDSRPEQPS	POSTPEPSPS	LQPAPNPQPA	150
PSNPIDEKLV	KEAVRKVGDG	YVFEENGVS	YIPAKDLSAE	TAAGIDSKLA	200
KQESLSHKLK	AKKTDLPSSD	REFYNKAYDL	LARIHQDLLD	NKGRQVDFEV	250
LDNLLERLKD	VSSDKVKLVD	DILAFLAPIR	HPERLGKPN	QITYTDEIQ	300
VAKLAGKYTT	EDGYIFDPRD	ITSDEGDAYV	TPHMTSHSWI	KKOSLSEAER	350
AAAQAYAKEK	GLTPPSTDHQ	DSGNTAKGA	EAIYNRVKAA	KKVPLDRMPY	400
NLQYTVKVN	GSLIIPHYDH	YHNIKFEWFD	EGLYEAPKGY	SLEDLLATVK	450
YYVEHPNERP	HSDNGFGNAS	DHV	(SEQ ID NO : 77)		473

FIGURE 42

CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	SENLTDPQVS	QKEGIAEQI	50
VIKITDQGYV	TSHGDHYHY	NGKVPYDALF	SEELLMKDPN	YQLKDADIVN	100
EVKGGYIIKV	DGKYVYVLKD	AAHADNVRTK	DEINRQKQEH	VKDNEKVNSN	150
VAVARSQGRY	TTNDGYVFNP	ADIIEDTGNA	YIVPHGGHYH	YIPKSDLSAS	200
ELAAAKAHLA	GKNMQPSOLS	YSSTASDNMT	QSVAKGSTSK	PANKSENLOS	250
LLKELYDSPS	AQRYSESDGL	VFDPAKIISR	TPNGVAIPHG	DHYHFIPYSK	300
LSALEEKIAR	MVPISGTGST	VSTNAKPNEV	VSSLGSLSSN	PSSLTTSKEL	350
SSASDGYIFN	PKDIVEETAT	AYIVRHGDHF	HYIPKSNQIG	QPTLPNNSLA	400
TPSPSLPINP	GTSHKHEED	GYGFDANRII	AEDESGFVMS	HGDHNHYFFK	450
KDLTEEQIKA	AQKHLEEVKT	SHNGLDSLSS	HEQDYPGNAK	EMKDLDKKIE	500
EKIAQIMKQY	GKRESIVVN	KEKNAIYPH	GDHHHADPID	EHPVVGIGHS	550
HSNYELFKPE	EGVAKKEGK	VYTGEELTNV	VNLLKNSTFN	NQNFTLANGQ	600
KRVSFSPPE	LEKKLGINML	VKLITPDGKV	LEKVSQKVF	EGVGNIANFE	650
LDQPYLPGQT	FKYTIASKDY	PEVSYDGTFT	VPTSLAYKMA	SQTIFYPFHA	700
GDTYLRVNPQ	FAVPKGTDAL	VRVDEFHGN	AYLENNYKVG	EIKLPIPKLN	750
QGTTRTAGNK	IPVTFMANAY	LDNQSTYIVE	(SEQ ID NO : 78)		780

FIGURE 43

CAYELGLHQA	QTVKENNRVS	YIDGKQATQK	TENLTPDEV	KREGINAEQI	50
VIKITDQGYV	TSHGDHYHY	NGKVPYDAII	SEELLMKDPN	YQLKSDIVN	100
EIKGGYVIKV	NGKYVYVLKD	AAHADNVRTK	EEINRQKQEH	SQHREGGTS	150
NDGAVAFARS	QGRYTTDDGY	IFNASDIIED	TGDAYIVPHG	DHYHYIPKNE	200
LSASELAAAE	AFLSGRENLS	NLRTYRRQNS	DNTPRTNWVP	SVSNPGTTNT	250
NTSMNSNTNS	QASQSNIDIS	LLKQLYKLPL	SQRHVESDGL	IFDPAQITSR	300
TARGVAVPHG	NHYHFIPYEQ	MSELEKRIAR	IPLRYRSNH	WVPDSRPEEP	350
SPQPTPEPSP	SPQPAPNPQP	APSNPIDEKL	VKEAVRKVG	GYVFEENGVS	400
RYIPAKNLSA	ETAAGIDSKL	AKQESLSHKL	GAKKTDLPSS	DREFYNKAYD	450
LLARIHQDLL	DNKGRQVDFE	ALDNLLERLK	DVSSDKVCLV	DDILAFLAPI	500
RHPERLGKPN	AQITYTDDDEI	QVAKLAGKYT	TEDGYIFDPR	DITSDEGDAY	550
VTPHMTSHSW	IKKDSLSEAE	RAAAQAYAKE	KGLTPPSTDH	QDSGNTEAKG	600
AEAIYNRVKA	AKKVPLDRMP	YNLQYTVVK	NGSLIIPHYD	HYHNIKFEWF	650
DEGLYEAPKG	YTLEDLLATV	KYYVEHPNER	PHSDNGFGNA		690

(SEQ ID NO : 79)

FIGURE 44

GTGAAGAAAA	CATATGGTTA	TATCGGCTCA	GTGCTGCCA	TTTTACTAGC	TACTCATATT	60
GGAAAGTTACC	AACCTGGTAA	GCATCATATG	GGTCTAGCAA	CAAAGGACAA	TCAGATTGCC	120
TATATTGATG	ACAGCAAAGG	TAAGGCAAAA	GCCCCTAAAA	CAAACAAAAC	GATGGATCAA	180
ATCAGTGCTG	AAGAAGGCAT	CTCTGCTGAA	CAGATCGTAG	TCAAAATTAC	TGACCAAGGC	240
TATGTGACCT	CACACGGTGA	CCATTATCAT	TTTTACAATG	GGAAAGTTCC	TTATGATGCG	300
ATTATTAGTG	AAGAGTTGTT	GATGACGGAT	CCTAATTACC	GTTTTAAACA	ATCAGACGTT	360
ATCAATGAAA	TCTTAGACGG	TTACGTTATT	AAAGTCAATG	GCAACTATTA	TGTTTTACCTC	420
AAGCCAGGTA	GTAAGCGCAA	AAACATTCTGA	ACCAAACAAC	AAATTGCTGA	GCAAGTAGCC	480
AAAGGAACCTA	AAGAAGCTAA	AGAAAAAGGT	TTAGCTCAAG	TGGCCCATCT	CAGTAAAGAA	540
GAAGTTGCGG	CAGTCAATGA	AGCAAAAAGA	CAAGGACGCT	ATACTACAGA	CGATGGCTAT	600
ATTTTATAGTC	CGACAGATAT	CATTGATGAT	TTAGGAGATG	CTTATTAGT	ACCTCATGGT	660
AATCACTATC	ATTATATTCC	TAAAAAGGAT	TTGTCTCCAA	GTGAGTAGC	TGCTGCACAA	720
GCCTACTGGA	GTCAAAAACA	AGGTCGAGGT	GCTAGACCGT	CTGATTACCG	CCCACACCA	780
GCCCCAGGTC	GTAGGAAAGC	CCCAATTCCCT	GATGTGACGC	CTAACCCCTGG	ACAAGGTCAT	840
CAGCCAGATA	ACGGTGGCTA	TCATCCAGCG	CCTCCTAGGC	CAAATGATGC	GTCACAAAAC	900
AAACACCAAAA	GAGATGAGTT	TAAAGGAAAA	ACCTTTAAGG	AACCTTTTAGA	TCAACTACAC	960
CGTCTTGATT	TGAAATACCG	TCATGTGGAA	GAAGATGGGT	TGATTTTTGA	ACCGACTCAA	1020
GTGATCAAAT	CAAACGCTTT	TGGGTATGTG	GTGCCATCATG	GAGATCATT	TCATATTATC	1080
CCAAGAAGTC	AGTTATCACC	TCTTGAAATG	GAATTAGCAG	ATCGATACCT	AGCTGGCCAA	1140
ACTGAGGACA	ATGACTCAGG	TTGAGAGCAC	TCAAAACCAT	CAGATAAAGA	AGTGACACAT	1200
ACCTTTCTTG	GTGATCGCAT	CAAAGCTTAC	GGAAAAGGCT	TAGATGGTAA	ACCATATGAT	1260
ACGAGTGATG	CTTATGTTTT	TAGTAAAGAA	TCCATTTCATT	CAGTGGATAA	ATCAGGAGTT	1320
ACAGCTAAAC	ACGGAGATCA	TTTCCACTAT	ATAGGATTG	GAGAACTTGA	ACAATATGAG	1380
TTGGATGAGG	TCGCTAACTG	GGTGAAAGCA	AAAGGTCAAG	CTGATGAGCT	TGCTGCTGCT	1440
TTGGATCAGG	AACAAGGCAA	AGAAAAACCA	CTCTTTGACA	CTAAAAAGT	GAGTCGCAAA	1500
GTAACAAAAG	ATGGTAAAGT	GGGCTATATG	ATGCCAAAAG	ATGGTAAGGA	CTATTTCTAT	1560
GCTCGTGATC	AACCTTGATT	GACTCAGATT	GCCTTTGCCG	AACAAGAACT	AATGCTTAAA	1620
GATAAGAAGC	ATTACCGTTA	TGACATTGTT	GACACAGGTA	TTGAGCCACG	ACTTGCTGTA	1680
GATGTGTCAA	GTCTGCCGAT	GCATGCTGGT	AATGCTACTT	ACGATACTGG	AAGTTCGTTT	1740
GTTATCCAC	ATATTGATCA	TATCCATGTC	GTTCGGTATT	CATGGTTGAC	GCGCGATCAG	1800
ATTGCAACAG	TCAAGTATGT	GATGCAACAC	CCCGAAGTTC	GTCCGGATGT	ATGGTCTAAG	1860
CCAGGGCATG	AAGAGTCAGG	TTCCGTTCATT	CCAAATGTTA	CGCCTCTTGA	TAAACGTGCT	1920
GGTATGCCAA	ACTGGCAAAT	TATCCATTCT	GCTGAAGAAG	TTCAAAAAGC	CCTAGCAGAA	1980
GGTCGTTTTG	CAACACCAGA	CGGCTATATT	TTGATCCAC	GAGATGTTTT	GGCCAAAGAA	2040
ACTTTTGAT	GGAAAGATGG	CTCCTTTAGC	ATCCCAAGAG	CAGATGGCAG	TTCATTGAGA	2100
ACCATTAATA	AATCTGATCT	ATCCCAAGCT	GAGTGGCAAC	AAGCTCAAGA	GTTATTGGCA	2160
AAGAAAAATA	CTGGTGATGC	TACTGATACG	GATAAAACCA	AAGAAAAGCA	ACAGGCAGAT	2220
AAGAGCAATG	AAAACCAACA	GCCAAGTGAA	GCCAGTAAAG	AAGAAAAAGA	ATCAGATGAC	2280
TTTATAGACA	GTTTACCAGA	CTATGGTCTA	GATAGAGCAA	CCCTAGAAGA	TCATATCAAT	2340
CAATTAGCAC	AAAAAGCTAA	TATCGATCCT	AAGTATCTCA	TTTCCAACC	AGAAGGTGTC	2400
CAATTTTATA	ATAAAATGG	TGAATTGGTA	ACTTATGATA	TCAAGACACT	TCAACAAATA	2460
AACCCTTAA	(SEQ ID NO : 80)					2469

FIGURE 45

VKKTYGYIGS	VAAILLATHI	GSYQLGKHHM	GLATKDNQIA	YIDDSKGKAK	50
APKTNKTMDO	ISAEEGISAE	QIVVKITDQG	YVTSHGDHYH	FYNGKVPYDA	100
IISEELLMTD	PNYRFKQSDV	INEILDGYVI	KVNGNYYVYL	KPGSKRKNIR	150
TKQQIAEQVA	KGTKEAKEKG	LAQVAHLSKE	EVAAVNEAKR	QGRTTDDGY	200
IFSPTDIIDD	LGDAYLVPHG	NHYHYIPKKD	LSPSELAAAQ	AYWSQKQGRG	250
ARPSDYRPTP	APGRRKAPIP	DVTPNPGQGH	QPDNGGYHPA	PPRPNDASQN	300
KHQREDFKKG	TFKELLDQLH	RLDLKYRHVE	EDGLIFEPTQ	VIKSNAFGYV	350
VPHGDHYHII	PRSQLSPLEM	ELADRYLAGQ	TEDNDSGSEH	SKPSDKEVTH	400
TFLGHRIKAY	GKGLDGKPYD	TSDAYVFSKE	SIHSVDKSGV	TAKHGDHFHY	450
IGFGELEQYE	LDEVANWVKA	KGQADELAAA	LDQEOGKEKP	LFDTKKVSrk	500
VTQDGKVGYM	MPKDGKDYFY	ARDQLDLTQI	AFAEQELMLK	DKKHRYRIDIV	550
DTGIEPRLAV	DVSSLPMHAG	NATYDTGSSF	VIPHIDHIHV	VPYSWLTRDQ	600
IATVKYVMQH	PEVRPDVWSK	PGHEESGSKI	PNVTPLDKRA	GMPNWQIIHS	650
AEVQKALAE	GRFATPDGYI	FDPRDVLAKI	TFVWKDGSFS	IPRADGSSLR	700
TINKSDLSQA	EWQQAQELLA	KKNTGDATDT	DKPKEKQAD	KSNENQOPSE	750
ASKEEKESDD	FIDSLPDYGL	DRATLEDHIN	QLAQKANIDP	KYLIFQPEGV	800
QFYNKGELV	TYDIKTLQOI	NPP	(SEQ	ID NO : 81)	823

FIGURE 46

GTGAAGAAAA	CATATGGTTA	TATCGGCTCA	GTTGCTGCCA	TTTTACTAGC	TACTCATATT	60
GGAAGTTACC	AAC TTGGTAA	GCATCATATG	GGTCTAGCAA	CAAAGGACAA	TCAGATTGCC	120
TATATTGATG	ATAGCAAAGG	TAAGGCAAAA	GCCCCTAAAA	CAAACAAAAC	GATGGATCAA	180
ATCAGTGCTG	AAGAAGGCAT	CTCTGCTGAA	CAGATCGTAG	TCAAAATTAC	TGACCAAGGT	240
TATGTGACCT	CACACGGTGA	CCATTATCAT	TTTTACAATG	GGAAAGTTCC	TTATGATGCG	300
ATTATTAGTG	AAGAGTTGTT	GATGACGGAT	CCTAATTACC	ATTTTAAACA	ATCAGACGTT	360
ATCAATGAAA	TCTTAGACGG	TTACGTTATT	AAAGTCAATG	GCAACTATTA	TGTTTACCTC	420
AAGCCAGGTA	GTAAGCGCAA	AAACATTGCA	ACCAAACAAC	AAATTGCTGA	GCAAGTAGCC	480
AAAGGAACTA	AAGAAGCTAA	AGAAAAAGGT	TTAGCTCAAG	TGGCCCATCT	CAGTAAAGAA	540
GAAGTTGCGG	CAGTCAATGA	AGCAAAAAGA	CAAGGACGCT	ATACTACAGA	CGATGGCTAT	600
ATTTT TAGTC	CGACAGATAT	CATTGATGAT	TTAGGAGACG	CTTATTTAGT	ACCTCATGGT	660
AATCACTATC	ATTATATTCC	TAAAAAGAT	TTGTCTCCAA	GTGAGCTAGC	TGCTGCACAA	720
GCTTACTGGA	GTCAAAAACA	AGGTCGAGGT	GCTAGACCGT	CTGATTACCG	CCCGACACCA	780
GCCCCAGGTC	GTAGGAAAGC	TCCAATTCCT	GATGTGACGC	CTAACCCCTG	ACAAGGTCAT	840
CAGCCAGATA	ACGGTGGCTA	TCATCCAGCG	CCTCCTAGGC	CAAATGATGC	GTCACAAAAC	900
AAACACCAAA	GAGATGAGTT	TAAAGGAAAA	ACCTTTAAGG	AACTTTTAGA	TCAACTACAC	960
CGTCTTGATT	TGAAATACCG	TCATGTGGAA	GAAGATGGGT	TGATTTTTGA	ACCGACTCAA	1020
GTGATCAAAT	CAAACGCTTT	TGGGTATGTG	GTGCCTCATG	GAGATCATT	TCATATTATC	1080
CCAAGAAGTC	AGTTATCACC	TCTTGAAATG	GAATTAGCAG	ATCGATACTT	AGCCGGTCAA	1140
ACTGAGGACA	ATGATTCAGG	TTCAGATCAC	TCAAAACCAT	CAGATAAAGA	AGTGACACAT	1200
ACCTTTCTTG	GTCATCGCAT	CAAAGCTTAC	GGAAAAGGCT	TAGATGGTAA	ACCATATGAT	1260
ACGAGTGATG	CTTATGTTTT	TAGTAAAGAA	TCCATTTCATT	CAGTGGATAA	ATCAGGAGTT	1320
ACAGCTAAAC	ACGGAGATCA	TTTCCACTAT	ATAGGATTG	GAGAACTTGA	ACAATATGAG	1380
TTGGATGAGG	TCGCTAACTG	GGTGAAAGCA	AAAGGTCAAG	CTGATGAGCT	TGCTGCTGCT	1440
TTGGATCAGG	AACAAGGCAA	AGAAAAACCA	CTCTTTGACA	CTAAAAAGT	GAGTCGCAAA	1500
GTAACAAAAG	ATGGTAAAGT	GGGCTATATT	ATGCCAAAAG	ATGGCAAGGA	CTATTTCTAT	1560
GCTCGTGATC	AAC TTGATTT	GACTCAGATT	GCCTTTGCCG	AACAAGAACT	AATGCTTAAA	1620
GATAAGAACC	ATTACCGTTA	TGACATTGTT	GACACAGGTA	TTGAGCCACG	ACTTGCTGTA	1680
GATGTGTCAA	GTCTGCCGAT	GCATGCTGGT	AATGCTACTT	ACGATACTGG	AAGTTCGTTT	1740
GTTATCCCTC	ATATTGATCA	TATCCATGTC	GTTCCGTATT	CATGGTTGAC	GCGCGATCAG	1800
ATTGCAACAA	TCAAGTATGT	GATGCAACAC	CCCGAAGTTC	GTCCAGATGT	ATGGTCTAAG	1860
CCAGGGCATG	AAGAGTCAGG	TTCGGTCATT	CCAAATGTTA	CGCCTCTTGA	TAAACGTGCT	1920
GGTATGCCAA	ATTGGCAAAT	CATCCATTCT	GCTGAAGAAG	TTCAAAAAGC	CCTAGCAGAA	1980
GGTCGTTTTG	CAACACCAGA	CGGCTATATT	TTCGATCCAC	GAGATGTTTT	GGCCAAAGAA	2040
ACTTTTGTAT	GGAAAGATGG	CTCCTTTAGC	ATCCCAAGAG	CAGATGGCAG	TTCATTGAGA	2100
ACCATTAATA	AATCTGATCT	ATCCCAAGCT	GAGTGGCAAC	AAGCTCAAGA	GTTATTGGCA	2160
AAGAAAAACG	CTGGTGATGC	TACTGATACG	GATAAACCCA	AAGAAAAGCA	ACAGGCAGAT	2220
AAGAGCAATG	AAAACCAACA	GCCAAGTGAA	GCCAGTAAAG	AAGAAGAAAA	AGAATCAGAT	2280

VKKTYGYIGS	VAAILLATHI	GSYQLGKHHM	GLATKDNQIA	YIDDSKGKAK	50
APKTNKTMDO	ISAEEGISAE	QIVVKITDQG	YVTSHGDHYH	FYNGKVPYDA	100
IISEELLMTD	PNYHFKQSDV	INEILDGYVI	KVNGNYVYVL	KPGSKRKNIR	150
TKQQIAEQVA	KGTKEAKEKG	LAQVAHLSKE	EVAAVNEAKR	QGRYTDDGY	200
IFSPTDIIDD	LGDAYLVPHG	NHYHYIPKPD	LSPSELAAQ	AYWSQKQGRG	250
ARPSDYRPTP	APGRRKAPIP	DVTPNPGQGH	QPDNGGYHPA	PPRPNDASQN	300
KHQRDEFK GK	TFKELLDQLH	RLDLKYRHVE	EDGLIFEPTQ	VIKSNAFGYV	350
VPHGDHYHII	PRSQLSPLEM	ELADRYLAGQ	TEDNDSGSDH	SKPSDKEVTH	400
TFLGHRIKAY	GKGLDGKPYD	TSDAYVFSKE	SIHSVDKSGV	TAKHGDHFHY	450
IGFGELEQYE	LDEVANWVKA	KGQADELAAA	LDQEQGKEKP	LFDTKKVS RK	500
VTKDGGKGYI	MPKDGKDYFY	ARDQLDLTQI	AFAEQELMLK	DKNHYRYDIV	550
DTGIEPRLAV	DVSSLPMHAG	NATYDTGSSF	VIPHIDHIHV	VPYSWLTRDQ	600
IATIKYVMQH	PEVRPDVWSK	PGHEESG SVI	PNVTPLDKRA	GMPNWQIIHS	650
AEVQKALAE	GRFATPDGYI	FDPRDVLAKE	TFVWKDGSFS	IPRADGSSLR	700
TINKSDLSQA	EWQQAQELLA	KKNAGDATDT	DKPKEKQQAD	KSNENQQPSE	750
ASKEEEKESD	DFIDSLPDYG	LDRATLEDHI	NQLAQKANID	PKYLIFQPEG	800
VQFYNKNGEL	VTYDIKTLQQ	INPP	(SEQ ID NO : 83)		824

FIGURE 48

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/31, 15/62, C07K 14/315, A61K 39/09		A3	(11) International Publication Number: WO 00/39299
			(43) International Publication Date: 6 July 2000 (06.07.00)
(21) International Application Number: PCT/CA99/01218			(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 20 December 1999 (20.12.99)			
(30) Priority Data: 60/113,800 23 December 1998 (23.12.98) US			
(71) Applicant (for all designated States except US): BIOCHEM PHARMA INC. [CA/CA]; 275 Armand Frappier Boulevard, Laval, Québec H7V 4A7 (CA).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): HAMEL, Josée [CA/CA]; (CA). BRODEUR, Bernard, R. [CA/CA]; 2401 Maritain, Sillery, Québec G1T 1N6 (CA). PINEAU, Isabelle [CA/CA]; 3035 Rue des Châtelets, Sainte-Foy, Québec G1V 3Y7 (CA). MARTIN, Denis [CA/CA]; 4728-G Gaboury, St-Augustin-DesMaures, Québec G3A 1E9 (CA). RIOUX, Clément [CA/CA]; 12 Croissant Barabé, Ile Bizard, Québec H9E 1J1 (CA). CHARLAND, Nathalie [CA/CA]; 4340 Rue du Rapide, Apt. 8, Charny, Québec J6X 3N6 (CA).			
(74) Agents: MURPHY, Kevin, P. et al.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montreal, Québec H3A 2Y3 (CA).			Published <i>With international search report.</i> (88) Date of publication of the international search report: 2 November 2000 (02.11.00)

(54) Title: STREPTOCOCCUS ANTIGENS

BVH11-2 SP64	BVH11 SP63	BVH11 JNL7/87	BVH11-2 JNL7/87	BVH11 WU2	BVH11-2 WU2	BVH11 A66	BVH11-2 A66	BVH11 P4241	BVH11-2 P4241	BVH11 Rx-1	BVH11-2 Rx-1	BVH11 SP64
181% S 86%	188% S 90%	188% S 91%	182% S 87%	180% S 85%	180% S 85%	180% S 85%	180% S 85%	180% S 85%	180% S 85%	188% S 91%	181% S 85%	BVH11 SP64
	187% S 90%	187% S 90%	198% S 98%	195% S 96%	196% S 97%	195% S 96%	196% S 97%	195% S 96%	196% S 97%	187% S 90%	194% S 95%	BVH11-2 SP64
		196% S 96%	188% S 91%	188% S 91%	187% S 90%	188% S 91%	187% S 90%	188% S 91%	187% S 90%	197% S 97%	189% S 91%	BVH11 SP63
			187% S 90%	187% S 91%	186% S 90%	187% S 91%	186% S 90%	187% S 91%	186% S 90%	196% S 96%	188% S 90%	BVH11 JNL7/87
				196% S 97%	197% S 98%	196% S 97%	197% S 98%	196% S 97%	197% S 98%	187% S 90%	194% S 95%	BVH11-2 JNL7/87
					198% S 98%	192% S 94%	198% S 98%	199% S 99%	198% S 98%	187% S 91%	192% S 94%	BVH11 WU2
						198% S 98%	199% S 99%	198% S 98%	199% S 99%	186% S 90%	193% S 95%	BVH11-2 WU2
							199% S 99%	1100% S 99%	199% S 99%	187% S 91%	192% S 94%	BVH11 A66
								199% S 99%	199% S 99%	186% S 90%	193% S 95%	BVH11-2 A66
									199% S 99%	187% S 91%	192% S 94%	BVH11 P4241

FOR THE PURPOSES OF INFORMATION ONLY

Codés used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/01218

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/31 C12N15/62 C07K14/315 A61K39/09

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CAB Data, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 18930 A (HUMAN GENOME SCIENCES INC ;CHOI GIL H (US); HROMOCKYJ ALEX (US); J) 7 May 1998 (1998-05-07) cited in the application SP103; SEQ ID NOs. 181 and 182; page 85, line 14 - line 42; claims 1-21; table I SEQ ID Nos. 65 and 66; ---	1-12
X	WO 98 18931 A (DOUGHERTY BRIAN A ;HUMAN GENOME SCIENCES INC (US); ROSEN CRAIG A () 7 May 1998 (1998-05-07) SEQ ID No.192 claims 1-20 SEQ ID No. 94 --- -/--	1-12

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "A" document member of the same patent family

Date of the actual completion of the international search

28 June 2000

Date of mailing of the international search report

24.07.00

Name and mailing address of the ISA
European Patent Office, P.O. 5818 Patentplan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hornig, H

INTERNATIONAL SEARCH REPORT

Int'l. Patent Application No
PCT/CA 99/01218

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 15675 A (GREEN BRUCE A ;CHENG QI (US); FINKEL DAVID J (US); MASI AMY W (US)) 1 April 1999 (1999-04-01) SEQ ID Nos.4 and 5; claims 1-61 ---	1-12
E	WO 00 06737 A (GILBERT CHRISTOPHE FRANCOIS GU ;HANSBRO PHILIP MICHAEL (GB); MICRO) 10 February 2000 (2000-02-10) page 41, line 57 -page 42, line 12 Clone 4138.1, SEQ ID Nos. 246; page 76, line 32 - line 38; claims 1-20 SEQ ID Nos. 194 and 206; ---	1-12
E	WO 00 06738 A (HANNIFFY SEAN BOSCO ;LE PAGE RICHARD WILLIAM FALLA (GB); WELLS JER) 10 February 2000 (2000-02-10) Clone ID 128-3.43, SEQ ID No.23; page 39, line 5 - line 47; claims 1-20 ---	1-12
E	WO 00 17370 A (GREEN BRUCE A ;CHENG QI (US); FINKEL DAVID J (US); MASI AMY W (US)) 30 March 2000 (2000-03-30) SEQ ID Nos.4 and 5 claims 1-35 -----	1-12

INTERNATIONAL SEARCH REPORT

Int. application No.
PCT/CA 99/01218

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

(1-32)partially, subjects 1 and 2;
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

☐ The additional search fees were accompanied by the applicant's protest

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: (1-32)-partially

An isolated polynucleotide encoding a polypeptide having at least 70%/90% identity to a second polypeptide having a sequence chosen from the BVH-3 family, respectively SEQ ID NOs.: 2,8,10,16,55-59,64-66, and 78 or fragments, analogs or derivatives thereof; said isolated polynucleotide encoding a polypeptide capable of generating antibodies having binding specificity for said polypeptide sequences; a vector comprising said polynucleotides; a host cell transfected with said vector; a process for producing said polypeptides; a chimeric polypeptide comprising two or more polypeptides chosen from said SEQ ID Nos. 2,8,10,16,55-59,64-66, and 78; a vaccine composition comprising said polypeptides; a method for therapeutic or prophylactic treatment of meningitis, otitis media, bacteremia or pneumonia infection in an individual; use of a vaccine composition for said treatment;

2. Claims: (1-32)-partially

Idem as subject 1, but limited to the BVH-11 family respectively SEQ ID NOs. 4,14,58,60-63,67-75,77 and 79;

3. Claims: (1-32)-partially

Idem as subject 1, but limited to the BVH-28 family respectively SEQ ID NO.6;

4. Claims: (1-32)-partially

Idem as subject 1, but limited to the BVH-71 family respectively SEQ ID NOs. 81 and 83;

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/01218

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9818930 A	07-05-1998	AU 5194598 A	22-05-1998
		AU 6909098 A	22-05-1998
		EP 0942983 A	22-09-1999
		EP 0941335 A	15-09-1999
		WO 9818931 A	07-05-1998
WO 9818931 A	07-05-1998	AU 5194598 A	22-05-1998
		AU 6909098 A	22-05-1998
		EP 0942983 A	22-09-1999
		EP 0941335 A	15-09-1999
		WO 9818930 A	07-05-1998
WO 9915675 A	01-04-1999	AU 9510598 A	12-04-1999
WO 0006737 A	10-02-2000	NONE	
WO 0006738 A	10-02-2000	NONE	
WO 0017370 A	30-03-2000	AU 6060899 A	10-04-2000

Form PCT/ISA/210 (patent family annex) (July 1992)

BNSDOCID: <WO__0039299A3_1_>

